

“Contraception in adolescents – regulatory considerations”

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List of Abbreviations

AAP	American Academy of Paediatrics
AR	Assessment Report
BMD	Bone Marrow Density
CHC	Combined Hormonal Contraceptives
ChMP	Committee for Medicinal Products for Human Use
CI	Contraceptive Injection
COC	Combined Oral Contraceptive
DGGG	German Society of Gynaecology and Obstetrics ("Deutsche Gesellschaft für Gynäkologie und Geburtshilfe")
DMPA	Depot MPA
DNG	Dienogest
D(E)XA	Dual-energy X-ray absorptiometry
DRSP	Drospirenone
DSG	Desogestrel
E2	Estradiol
EE	Ethinylestradiol
ETG	Etonogestrel
EU	European Union
GVP	Good Pharmacovigilance Practice
HMA	Heads of Medicines Agencies
IUD	Intra Uterine Device
LNG	Levonorgestrel
MAH	Marketing Authorisation Holder
MPA	Medroxyprogesterone Acetate
MRI	Mutual Recognition Index
NCA	National Competent Authority
NET	Norethisterone
NGMN	Norelgestromin
OC	Oral Contraceptive
PAM	Post Authorisation Measure
PDCA	Paediatric Committee
PDR	Physician's Desk Reference
PI	Product Information
PID	Pelvic Inflammatory Disease
PIP	Paediatric Investigation Plan
POP	Progestogen-only Pill
PL	Package Leaflet
RCT	Randomised Controlled Trial
SmPC	Summary of Product Characteristics
STD	Sexually Transmitted Diseases
WHO	World Health Organisation

1. Introduction

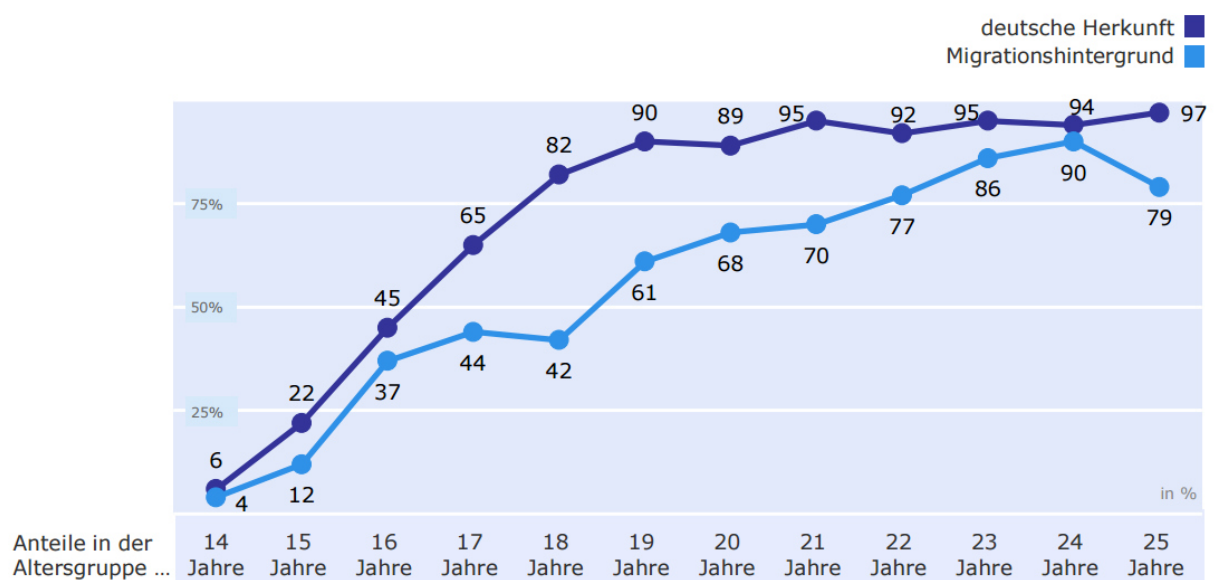
1.1. Contraception in adolescents

1.1.1. Medical need

In Germany, according to a recent report on adolescent sexuality (1) published by the German Federal Centre for Health Education (BZgA) in 2015, approximately 30% of the adolescents between 14-17 years do have first coital experiences. Among young adults (18-25 years), the percentage rises up to 86%.

There even is a minority of about 5% of the adolescent girls younger than 14 years who have experienced first sexual intercourse (coitus). The percentage of experienced adolescents is then constantly growing, even 20% of the 15-year-old German girls and 66% of the 17-year-old German girls have already had sexual intercourse. The percentage of sexually active adolescent girls with migration background tends to be somewhat lower.

Figure 1: Percentage [%] of sexually active girls/women by age [years]



Dark blue: German background

Light blue: Migration background

Source: Heßling, Angelika and Bode, Heidrun. *Jugendsexualität 2015. Die Perspektive der 14-bis 25-Jährigen. Ergebnisse einer aktuellen Repräsentativen Wiederholungsbefragung. 2015, pg.109 (1)*

The BZgA report has investigated how the percentage of sexually active adolescents has changed over the time. Covering a period beginning in 1980 up to 2014, a trend towards first experiences at a younger age can be seen. This trend, however, is not dramatic. The highest percentage could be seen in 2005, since then it has been decreasing.

Table 1: Percentage [%] of sexually active adolescent girls and boys

	1980	1994	1996	1998	2001	2005	2009	2014
Mädchen	25	29	33	38	35	39	37	34
Jungen	15	29	27	29	31	33	31	28

Anteile in %

Mädchen: Adolescent girls (14-17 years)

Jungen: Adolescent boys (14-17 years)

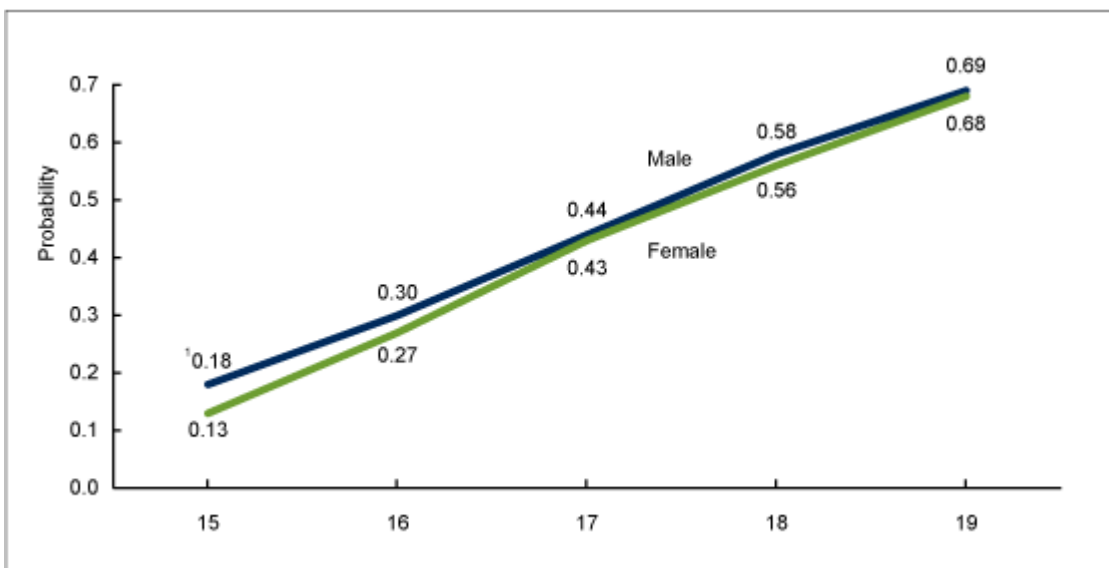
Source: Heßling, Angelika and Bode, Heidrun. *Jugendsexualität 2015. Die Perspektive der 14-bis 25-Jährigen. Ergebnisse einer aktuellen Repräsentativen Wiederholungsbefragung. 2015, pg.112 (1)*

There seem to be slight differences in terms of age of sexual initiation in the European Union (EU). A publication by Kraus et al. states as follows:

“The lowest age of sexual initiation was in Germany with the sexual activity of girls starting at the age of 14.5 [...]. In the remaining countries, this age was not so diversified. English girls claimed to have begun sexual activity at the age of 14.7 [...]. In France, Ukraine and Poland the age of initiation was [...] 16.7, 15.6 and 16.6 for girls.”

In the USA, according to information based on a national survey of family growth performed between 2011 and 2013 and published on the homepage of the Center for Disease Control and Prevention (2), the probability of having had sex was 13% in the population interviewed at the age of 15. The results show that the percentage of sexually active female adolescents has increased steadily since then.

Figure 2: Probability of having had sex by ages 15, 16, 17, 18, and 19 for males and females: United States, 2011–2013



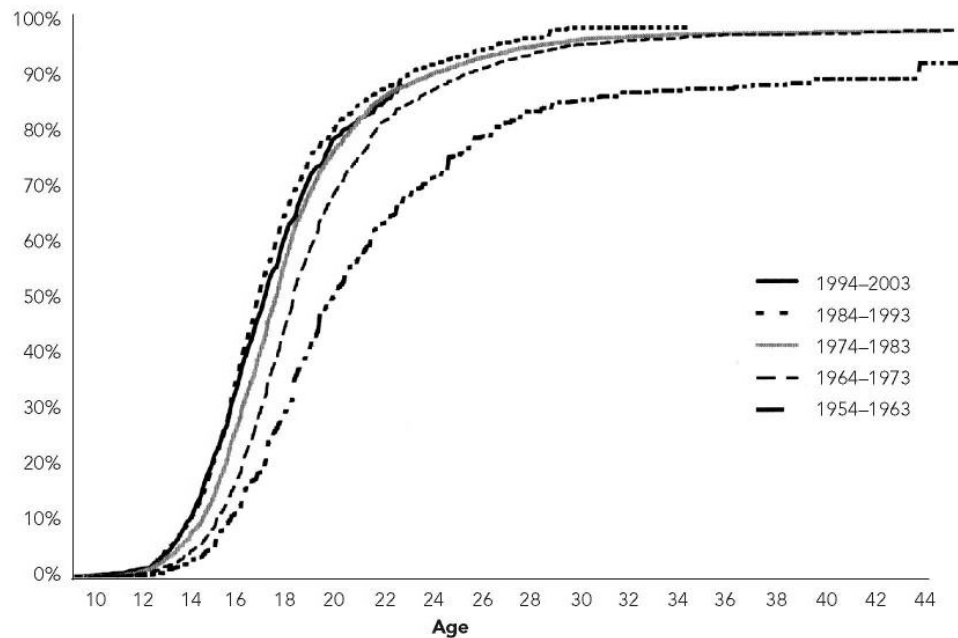
Blue graph: Male adolescents

Green graph: Female adolescents

Source: Homepage Center for Disease Control and Prevention, USA (2)

It seems that the probability of having sex at a younger age has not significantly changed over the last decades in the USA.

Figure 3: Percent of women in the USA who had had premarital sex by specific ages, sorted by decade where they turned 15 years



Source: Lawrence B. Finer et al.; *Trends in Premarital Sex in the United States, 1954-2003* (3)

This is in line with the information published by the CDC (2) stating that the mean age of first intercourse after menarche for women aged 15-44 years has not significantly changed in the last decade (between 2002 and 2013).

The cited reports show that there has been - and there still is - a relevant percentage of sexually active adolescents for whom adequate contraceptive measures are needed. The situation seems to be similar within the EU and the USA. Therefore, it can be no doubt that there is a medical need for safe and effective contraceptive methods for the adolescent population. A detailed, systematic investigation of the sexual behaviour in the adolescent population is beyond the scope of this thesis.

The different contraceptive options and their adequacy for use in the adolescent female population will be discussed in the subsections below.

1.1.2. Current contraceptive use in the adolescent population

According to an outdated guideline on contraception (4) of the German Society of Gynaecology and Obstetrics (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe; DGGG) which will be discussed more detailed below, 41% (17.2 million) of all women in Germany use some kind of contraceptive measures. Among all women in their reproductive age (here 14-44 years),

19% (3.2 million) are between 14-20 years of age. The following table represents an excerpt of information which can be found in the DGGG 2010's guideline:

Table 2: Current methods of contraception in Germany

	Million	%	Reference system
Women of reproductive age (14-44 years)	17.2	41%	All women
Women 14-20 years	3.2	19%	All women of reproductive age
Contraception			
Oral Contraceptives (OC), total	6.6	38.5%	All women of reproductive age
Women < 20 years (14-19 years), taking OCs	1.5	55%	All women between 14-19 years (2.8 million)
OC < 50 µg EE	6.2	36.1%	All women of reproductive age
OC > 50 µg EE	0.4	2.3%	All women of reproductive age
Intravaginal ring	approx. 0,13	approx. 0.8%	All women of reproductive age
Hormonal patch	no data available		All women of reproductive age
Estrogen free ovulation inhibitors	approx. 0,19	approx. 1.1%	All women of reproductive age
Copper IUD	approx. 1	approx. 6%	All women of reproductive age
Hormonal IUD	approx. 1	approx. 6%	All women of reproductive age
Progestogen-only pill (POP, "Minipille")	approx. 0.01	approx. 0.06%	All women of reproductive age
3-monthly contraceptive injection	approx. 0.2	approx. 1%	All women of reproductive age
Hormonal implant	approx. 0.15	approx. 0.9%	All women of reproductive age
Emergency postcoital contraception ("Pille danach")	0.2	1%	All women of reproductive age
Condoms	4.8	28%	All women of reproductive age
Spermicides	no data available		All women of reproductive age
Natural family planning	1.4	8%	All women of reproductive age
Sterilisation			
• Women	1.4	8%	All women of reproductive age
• Men	0.45	2%	All men

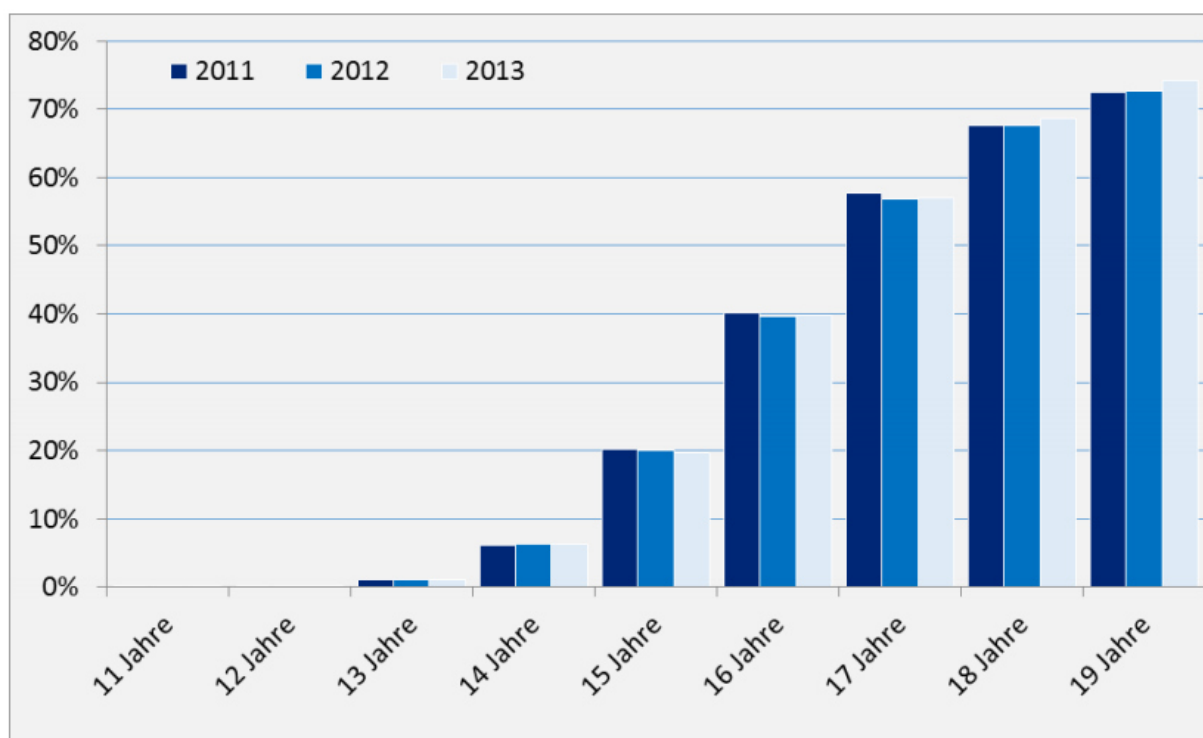
Source: modified after DGGG Guideline on contraceptives 2010 (4)

According to the table cited above, there were approximately 1.5 million women between 14-19 years of age taking OCs. Even though the data for contraceptive methods other than oral contraceptives (OCs) are not further stratified by age, it is obvious that contraceptive measures

other than OCs are used only by a minority of all women. Condoms are used by 28% of all women of reproductive age. This might, however, be also due to the necessity of being also protected against sexually transmitted diseases (STDs) like HIV, Hepatitis and HPV. Taking this into account, it seems obviously advisable to use a barrier method in addition to hormonal contraceptives, especially if not in a stable relationship.

The “Pillenreport 2015” (5) states some more recent data for OCs use stratified by age and confirms the data discussed above. To be more precise, it confirms that OC are used by a considerable subset of adolescent girls in Germany.

Figure 4: Percentage of women with an OC prescription between 2011 and 2013 stratified by age (database: women insured at the TK health insurance)



Source: *Pillenreport 2015* (5)

X-axis: age [years]

Y-axis: percentage of women in certain age group (of women insured at the TK health insurance) [%]

The absolute figures and percentages might have slightly changed in the years after this guideline of the German Society of Gynaecology and Obstetrics or the TK report have been published. For example, the percentage of women using emergency postcoital contraception might have increased after the over-the-counter (OTC) switch as they can now be bought without prescription. The current contraceptive use in Germany will not be compared to the use in other countries of the EU or the USA. As was stated in the section on medical need above, a more detailed description of the pattern of use of contraceptives is beyond the scope of this thesis. The focus is rather to investigate if issues prior identified to be of special

relevance for the efficacy and safety of contraceptives in the adolescent population (section 1.1.3-1.1.4) have been adequately covered pre- and post-marketing in the regulatory context.

1.1.3. General Recommendations of Medical Scientific Societies (DGGG, WHO)

The DGGG is currently updating its guideline on contraception. The outdated guideline “Empfängnisverhütung” is dated September 2010 (4).

In this guideline, among others, recommendations for choosing adequate contraceptive methods for adolescent girls below the age of 18 are given. According to the guideline, the method of choice for young adolescent girls are OCs. Stated advantages are their high contraceptive efficacy, good cycle control and the low risk of pelvic inflammatory diseases (PIDs). According to the guideline, another advantage is the possibility to use OCs with antiandrogenic properties to concomitantly treat acne, which is stated to be a common problem in this age group (30-40% of all women below 20 years of age). It is further reasoned that OCs were shown to protect against certain diseases like ovarian- and endometrial cancer or polycystic ovarian syndrome and the treatment related overall risks are rather low.

For adolescent girls without signs of androgenisation, as alternative options, the use of intravaginal rings (e.g. NuvaRing) or hormonal patches (e.g. EVRA) is recommended.

Spermicides and condoms as possible options are also discussed. According to the guideline, the use of condoms, however, is often hampered by compliance and handling issues in this age group and condoms are not recommended as exclusive method. However, concomitant use of condoms is recommended to protect against STIs.

It is advised against the use of natural family planning methods as the menstrual cycle is often not yet stable and adolescent girls will often be unable to reliably survey the physiological changes during their menstrual cycle.

Sterilisation is not an option and prohibited by law in Germany (§1631c BGB), even with permission of parents or any legal guardian.

Remarkably, the guideline defines the next subpopulation for whom recommendations are given as women between 16-30 years of age. Obviously, there is a certain overlap for women between 16-18 years. It can, however, be assumed that most women are more or less fully developed when they are 16 and the focus of the current work lies on very young women who can reasonably be expected to differ from adult women in some e.g. physiological and anatomical aspects. In comparison to the recommendations for very young adolescents, the choice of adequate contraceptives in this older age group will have to start to also consider

potential cardio-vascular risk factors. Notably, rare reports of thrombotic events have also been published for young adolescents (6).

Copper IUDs are only recommended if other contraceptive measures have been shown to be inadequate (later line). This is justified by the fact that the use of copper IUDs was shown to be connected to a higher risk for STDs when users do not live in monogamous relationships and have frequently changing sexual partners. Some STDs can lead to permanent sterility, e.g. via pelvic inflammation. Young adolescent girls should only use copper IUDs if they live in a monogamous relationship, have no history of PIDs and if other contraceptive methods are not suitable.

The DGGG guideline on contraceptives includes a subsection on oral hormonal contraceptives and osteoporosis. The potential detrimental influence of OCs on bone metabolism and possible effects on bone marrow density (BMD) is discussed based on the results of 5 publications published between 1995 and 2003. In summary, the guideline concludes that the only contraceptive method which was shown to have a negative influence on BMD were 3-monthly contraceptive injections containing medroxyprogesterone acetate (MPA). In consequence, the subsection on MPA containing depot preparations states “decrease of BMD at long term use in very young women” as disadvantage of this contraceptive method.

The World Health Organisation (WHO) published the fifth edition of “Medical eligibility criteria for contraceptive use” in 2015 (7). According to this comprehensive publication, “*in general, adolescents are eligible to use all the same methods of contraception as adults [...]*” (7). Concerns with regard to a potential influence of hormonal contraceptives on BMD and fracture rates have been extensively discussed, also focussing on adolescents. It was concluded that the evidence on whether CHC use influences the fracture risk is inconsistent and that CHC use may decrease BMD in adolescents. This was found to be especially true for OC with very low doses of ethinylestradiol (< 30 µg EE).

The WHO publication includes a tabulated summary of all recommendations, the part on suitability of different contraceptive methods sorted by age is cited below:

Table 3: Tabulated summary of WHO recommended contraceptive methods 2015 by age

SUMMARY TABLE						
COC/P/CVR	CIC	POP	DMPA/NET-EN	LNG/ETG/IMPLANTS	CU-IUD	LNG-IUD
NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a	NA ^a
Menarche to < 40=1 ≥ 40=2	Menarche to < 40=1 ≥ 40=2	Menarche to < 18=1 18-45=1 > 45=1	Menarche to < 18=2 18-45=1 > 45=2	Menarche to < 18=1 18-45=1 > 45=1	Menarche to < 20=2 ≥ 20=1	Menarche to < 20=2 ≥ 20=1

Categories:

- 1: A condition for which there is no restriction for the use of the contraceptive method
- 2: A condition where the advantages of using the method generally outweigh the theoretical or proven risks
- 3: A condition where the theoretical or proven risks usually outweigh the advantages of using the method
- 4: A condition which represents an unacceptable health risk if the contraceptive method is used

CIC: combined injectable contraceptive; COC: combined oral contraceptive (pill); Cu-IUD: copper-bearing intrauterine device; CVR: combined contraceptive vaginal ring; DMPA: depot medroxyprogesterone acetate; ETG: etonogestrel; LNG: levonorgestrel; LNG-IUD: levonorgestrel-releasing intrauterine device; NET-EN: norethisterone enanthate; P: combined contraceptive patch; POP: progestogen-only pill

Source: modified after Medical eligibility criteria for contraceptive use WHO 2015 (7)

Noteworthy, copper IUDs and levonorgestrel (LNG)-IUDs have been rated as contraceptive methods for which the advantages of using the method generally outweigh the theoretical or proven risks in the age group “menarche to below 20”. Regarding copper IUDs, this differs somewhat to the recommendations given by the DGGG. The recommendations of the WHO have to consider the worldwide situation and the benefit/risk balance for different contraceptive methods. They can reasonably be expected to differ between countries depending on the healthcare system and the quantity and quality of the available medical care. In these circumstances, it must be considered that pregnancy itself can represent a serious medical risk, especially in countries with less developed medical care. Contraceptive methods like long term depot MPA injections can enable access to highly effective contraceptive protection independent of further logistical or compliance issues. This benefit might be assessed to be more relevant in circumstances where medical risks associated with pregnancies can be foreseen.

1.1.4. Key issues specific to hormonal contraceptives in adolescents according to selected scientific publications

As treatment guidelines of medical scientific societies discussed above focus on rather practical advices how to choose the adequate treatment for an individual woman, this section attempts to report on a somewhat broader approach looking into scientific publications with focus on efficacy and safety of hormonal contraceptives in postmenarcheal adolescent girls.

An internet research in PubMed, Google Scholar and Google was performed to find reviews assessing the suitability of different contraceptive measures in women below 18 years of age. As discussed in section 1.1 and 1.2, there is a relevant need and usage of contraceptives by women clearly below 18 years. Young postmenarcheal adolescent girls will often not yet be fully grown. Efficacy and safety of different hormonal and non-hormonal contraceptive measures could reasonably be expected to differ among young adolescent girls and adult women due to physiological and psychological reasons.

A publication by Ludwig et al. (8) discusses at what age contraception should be initiated and how long it should be continued. For this thesis, answers to the first part of the question are relevant and according to the author, this question is easy to be answered. This should be the time “when it is necessary” (to protect against unwanted pregnancy). The publication discusses cardio-vascular, oncological risks and risk associated to bone metabolism and longitudinal growth. Cardiovascular risks are regarded to be of minor concern in adolescents without risk factors (e.g. smoking, obesity, thrombophilia or risk factors in the family anamneses). In the author’s view, oncological risk factors are negligible in terms of increase of the absolute (not relative) risk. Although it was stated that the majority of the clinical studies indicate that COCs seem to influence the peak bone accrual negatively, it was concluded that this seems clinically irrelevant if taking a look into the results of 2 clinical studies on fracture rates in later life. Although no valid clinical data are available, the author further concludes that no negative effect of COCs on longitudinal growth should be expected. In summary, the author recommends COCs with 30 µg of EE, as compared to low dose COCs with 20 µg EE, these seem to more often induce a regular menstrual cycle. Irregular cycles with breakthrough spotting and bleeding shall be associated with less compliance. The recommendation to preferably prescribe a COC with a higher EE content of 30 µg for young women is in line with a publication by Wildt et al., that discourages the use of depot injections and POPs in adolescent girls because of known detrimental effects for depot injections and unknown effects for POPs, respectively (9). If there is indeed an advantageous effect of higher dosed COCs with 30 µg EE on bone metabolism and consequently BMD compared to lower dosed COCs with 20 µg EE is, however, still debateable as there is a lack of clinical data from adequately designed, randomised controlled trials (RCTs) (10). It is interesting that in an older publication of 2006 in the same journal (11), discussing this issue “to be controversial” for COCs (not depot MPA), COCs with 20 µg EE have been recommended as first choice for otherwise healthy adolescents. This publication also discusses the suitability of copper IUDs. The authors recommend to consider these only if other methods cannot be used. They reason that even if newer clinical data don’t seem to indicate higher rates of induced PIDs in nulliparous women, data on PIDs in adolescents would be too sparse to be reliable.

A publication of the year 2013 by G. Merki-Feld (12) discussing the adequacy of different contraceptive methods in adolescents also recommends the use of COCs containing 30 µg EE and LNG because of potential advantages I.) compared to low-dose COCs in terms of the effects on bone metabolism and II.) with regard to cardio-vascular risks compared to 3rd generation COCs containing progestogens like desogestrel (DSG) or drospirenone (DRSP). According to Merki-Feld, criteria for suitability of contraceptive methods in adolescent girls are:

- a high contraceptive efficacy
- a low risk for serious adverse events
- induction of a stable menstrual cycle
- easy to use
- protection against STDs – not achievable via hormonal contraception
- smallest possible influence on peak bone mass accrual

Medicinal products containing a progestogen like POPs, Depo-injections and implants are also discussed. As discussed in the review, break-through spotting and bleeding as well as amenorrhoea are often not well accepted in adolescent girls and this is one of the reasons why POPs are not regarded to be the first choice in adolescents. However, also according to Merki-Feld et al., the decreased risk for cardio-vascular adverse events make POPs a reasonable choice for adolescents with risk factors like obesity, migraine and others. Depo-injections might be the preferred choice in adolescents that are e.g. unable to be compliant to daily intake instructions or in whom an induced amenorrhoea might be desirable. The potential detrimental effects need, however, to be considered. Stated reasons for a rather reluctant use of IUDs in adolescent girls are that adolescents belong to a population at risk for STDs, the placement of the IUD in the uterine cavity is regarded to be a (heavy) burden for young nulliparous adolescents with a small uterus and compared to adults, the rates for expulsion or dislocation of the device are increased.

The induction of a regular cycle and probably a decreased possible influence on bone metabolism are also stated reasons to choose COCs with 30 µg EE in a publication by Möstl et al. (13). Similarly, contraceptives containing only a progestogen are normally not regarded to be the first choice in normal circumstances (e.g. no cardio-vascular risk factors) because of their unfavourable effects on bleeding pattern and their effects on E2 levels and BMD. In addition, a possible negative effect on acne and seborrhoea are also quoted in this publication.

Ornstein et al. (14) highlight that beside serious adverse events, “*minor bothersome effects*” can also affect compliance and be one of the reason for high discontinuation rates seen in adolescents. As discussed by other authors, irregular bleeding and amenorrhoea are stated to be not acceptable for many teenagers. The authors argue that methods like transdermal patches or intravaginal rings might be associated with greater compliance at the first glance,

as they do not require adherence to daily regimen. However, possible drawbacks like visibility of the patch or difficulties with insertion of the intravaginal ring are also discussed.

The American Academy of Pediatrics (AAP) published two thorough articles about contraception for adolescents in 2014. The “*Policy Statement*” (15) “*provides the paediatrician with a description and rationale for best practices in counselling and prescribing contraception for adolescents*”. Further details can be found in an accompanying “*Technical Report*” (16). One important – however, somehow self-evident - statement is, that counselling should be based on *typical use* rather than *perfect use*. This would, however, only be possible, if there were reliable real world data on *typical use* available, like e.g. demanded by an FDA Advisory Committee publication (17) discussed later in section 1.1.5.2. The AAP Policy Statement cites clinical studies that indicate typical use failure rates of 9% in adults for the USA and speculates that typical use failure rates may even be higher in US American adolescents.

The recommendations are mainly in line with what was discussed by other authors in the publications discussed above. One of the additional aspects discussed might be that POPs that do not suppress ovulation, e.g. containing LNG, need stringent adherence to the 24h dosing interval [+/- 3h] and might therefore be a less favourable choice in adolescents without safety concerns about estrogen use.

Summarising the published reviews cited above, it can be stated that COCs containing 30 µg EE in combination with a progestogen known to have comparably favourable effects on the cardio-vascular risk (e.g. like LNG) seem to be the method of choice for healthy adolescent girls. However, it seems that possible effects on BMD have not yet been adequately studied and the often recommended choice of COCs containing 30 µg EE over low dose COCs containing 20 µg EE seems not to be based on adequate clinical studies. As the clinical more relevant effect is a detrimental influence on the fracture rate, potential effects will probably become firstly obvious at the time when actual users will have reached a considerable age. Noteworthy, older generations of COCs had much higher EE content of 50 µg EE or more (first-generation estrogen dosages started at 150 µg in the 1960s (18)). Current generation OCs have a lower EE content of 30 µg or 20 µg taking into account the acquired knowledge of the importance of the estrogen component on unfavourable cardio-vascular effects.

Table 4: Summary of potential efficacy and safety issues of hormonal contraceptives with special relevance in adolescent girls

Contraceptive method	Possible adverse events and/or advantages	Recommendations according to published treatment guidelines and reviews
COCs (30 µg EE)	- Lowered endogenous E2 level due to ovarian suppression	Limited data would rather question clinically relevant effects on bone

Contraceptive method	Possible adverse events and/or advantages	Recommendations according to published treatment guidelines and reviews
	<p>without sufficient external EE administration, leading to detrimental effects on bone metabolism.</p> <p>- Inducing a favourable bleeding pattern in the majority of the women which might be of special relevance in women with dysmenorrhea or heavy menstrual bleeding</p>	<p>metabolism and peak bone mass accrual for COCs containing 30 µg EE.</p> <p>They are in the majority of recommendations regarded to be the first choice for contraception in adolescents without cardiovascular risk factors.</p> <p>Combinations with a lower incidence of VTEs (e.g. EE + LNG) should be preferred to 3. generation COCs (e.g. EE + DRSP).</p>
COCs (20 µg EE)	<p>- Lowered endogenous E2 level due to ovarian suppression without sufficient external EE administration compared to COCs with 30 µg EE, leading to detrimental effects on bone metabolism.</p>	<p>Based on limited data on possible detrimental effects on bone metabolism and peak bone mass accrual as well as a more favourable bleeding pattern, COCs with 30 µg and not 20 µg EE should be preferably prescribed for contraception in adolescents without cardiovascular risk factors.</p>
POP (LNG)	<p>- Unfavourable bleeding pattern</p> <p>-Unfavourable posology (every 24 +/- 3h, decreased efficacy and back-up contraception if more than 3 h late)</p>	<p>The unfavourable bleeding pattern might result in non-compliance or early discontinuation. Non-compliance to the strict posology requirements could lead to a higher rate of user failures.</p> <p>LNG containing POPs should be preferably prescribed for contraception in adolescents with cardiovascular risk factors that are not eligible for COCs or DSG containing POPs.</p>
POP (DSG)	<p>- Unfavourable bleeding pattern</p> <p>- Lowered endogenous E2 level due to ovarian suppression without external EE administration like in COCs, leading to detrimental effects on bone metabolism</p>	<p>The unfavourable bleeding pattern might result in non-compliance or early discontinuation.</p> <p>DSG containing POPs should be preferably prescribed for contraception in adolescents with cardiovascular risk factors that are not eligible for COCs. The possible detrimental effects on bone metabolism and peak bone mass accrual should be considered.</p>

Contraceptive method	Possible adverse events and/or advantages	Recommendations according to published treatment guidelines and reviews
Depot-injection	<ul style="list-style-type: none"> - Lowered endogenous E2 level due to ovarian suppression without external EE administration like in COCs, leading to detrimental effects on bone metabolism. 	<p>Detrimental effects on bone metabolism and peak bone mass accrual have been seen in clinical studies, effects on fracture rates in later life are controversial. Due to the known possible risks with regard to the loss of BMD, only indicated if other contraceptive methods are considered unsuitable or unacceptable, e.g. in women with compliance issues [Black-Box warning in the USA].</p>
Intravaginal ring	<ul style="list-style-type: none"> - Increased discomfort and problems with insertion due to anatomical differences 	<p>Non-compliance and early discontinuation might be higher than in adults. However, according to the AAP Technical Report (16), <i>“the ring has a comparable typical-use failure rate (9%), risks, and benefits as other combined hormonal methods [...]”</i></p>
Transdermal patch	<ul style="list-style-type: none"> - Higher EE exposure compared to COCs (adolescent and adults) - Inconsistent results on bone health with <i>“findings in adults more reassuring than those in adolescents”</i> (16) - Higher discontinuation rates compared to COCs 	<p>There is possibly an increased risk of VTEs compared to COCs (odds ratio 1.2-2.2, Black-Box warning in the USA for <i>Ortho EVRA</i> (19)). In addition, discontinuation rates are higher than in COCs and effects on bone metabolism are not adequately investigated. Rather not a first line choice.</p>
IUDs (hormonal)	<ul style="list-style-type: none"> - Higher expulsion rates in adolescents - Induced PIDs which might result in infertility in the worst case - Lowered endogenous E2 level due to ovarian suppression without external EE administration like in COCs, leading to detrimental effects on bone metabolism. 	<p>According to the AAP (16), hormonal IUDs are in general an appropriate method for adolescents. The small increase of pelvic infections are regarded to be a result of the procedure, which could be dealt with if women are adequately examined for STDs and the physician is well trained in the application procedure. Adolescent specific data are, however, regarded to be limited.</p>
IUDs (copper)	<ul style="list-style-type: none"> - Higher expulsion rates 	<p>Similar to hormonal IUPs, however, less concerns about possible detrimental</p>

Contraceptive method	Possible adverse events and/or advantages	Recommendations according to published treatment guidelines and reviews
	- Induced PIDs which might result in infertility in the worst case	effects on bone metabolism, as copper IUDs do not interfere with the ovarian activity.

Source: The information cited in the table are taken from the publications cited and discussed in section 1.1.4 above.

1.1.5. Regulatory view on the requirements for the registration of hormonal contraceptives

1.1.5.1. EMA

Official European guidance on the regulatory requirements for the registration of hormonal contraceptives was issued in the year 2000 and last updated in 2005 by the Committee for Medicinal Products for Human Use (ChMP). The *Guideline on Clinical Investigation of Steroid Contraceptives in Women* (20) covers different aspects with regard to design and conduct of clinical pharmacological, efficacy and safety studies. It is applicable for short-acting and long-acting hormonal contraceptives containing only a progestogen or a combination of progestogens and estrogens. Named examples other than OCs are “*implants, injectables, transdermal systems, intravaginal and medicated hormone releasing intrauterine devices (IUDs)*” (20). The guideline emphasises that contraceptives need to have a very low risk to have a favourable risk/benefit balance as they are used for prophylactic/preventive purposes by healthy individuals.

No specific guidance on evaluation of efficacy and safety in the adolescent population is given. Some general advices may, however, be of special relevance pertaining to this issue. As already mentioned above and discussed in more detail in the discussion section below, estrogens play a pivotal role for bone metabolism. The guideline on evaluation of contraceptives specifies the need to investigate the influence of the new contraceptive on ovarian function. Plasma concentrations of ovarian steroids (including estrogens) need to be measured for at least two cycles. Plasma sampling should be frequent enough not to miss hormonal peaks and to give reliably estimates of their duration. In the subsection on metabolic effects, the guideline states that “*for products not containing an estrogen and suppressing estrogen secretion from the ovaries, the effect on bone mineral density and/or bone metabolism should be studied with validated methods*” (20).

With respect to the demography of the population to be studied, it is stated that it should be carefully described (including information on age) and a possible heterogeneity of fertility (e.g. between younger and older women) should be covered by separate estimates and/or specific

studies. In general, the population studied should be “*sufficiently representative*” for all “*key studies*”.

For information on important safety aspects like cancer, cardiovascular events or venous thromboembolism (VTE), it is reasoned that the studied populations are generally too small to provide reliable results. This would be interpreted to also emphasize on the need for appropriate post marketing surveillance, which should be defined in a comprehensive way in an adequate Risk Management Plan (RMP).

Cycle control analysis investigating episodes of bleeding and spotting should cover a period of 90 days and should be conducted in line with respective WHO recommendations.

The EMA Guideline on good pharmacovigilance practice (GVP) module V (21) also discusses issues specific to the paediatric population. The RMP needs to cover details on “*how [...] specific paediatric aspects will be addressed*”, e.g. as children (here defined “*from birth to 18 years*”) might be a “*population not studied in clinical trials*”. One of the tasks of the RMP is to define safety concerns. Safety concerns can be important identified risks, important potential risks and missing information. The Pharmacovigilance Plan should also discuss on how known safety concerns will be further characterised and how it could be elucidated if a potential safety concern is real or not. Additional pharmacovigilance activities might also encompass comparative clinical trials. With regard to the key question of this thesis, if there are missing information on potential safety issues in the paediatric, in this case adolescent population, it might be necessary to further investigate them post-marketing, as stated in the EMA PV Guideline (21): “[...] *the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.*” If the need for further studies is identified within the MAA procedure, and it is assessed that it can be justified to postpone such studies to a time post authorisation, a competent authority can impose such safety studies as a post authorisation measure (PAM).

Taking a closer look on the regulatory requirements for the registration of hormonal contraceptives in the EU, especially for contraceptives also administered to adolescent girls, one could think that the Paediatric Committee (PDCO) could play a pivotal role in this circumstances. As stated in the EMA document “*Rules of procedure of the Paediatric Committee (PDCO)*” (22) and underlined by the author, “*the Paediatric Regulation, lays down obligations, rewards and incentives for the development and placing on the market of medicines for use in children, and EU procedures to ensure that medicines used to treat children are subject to ethical research of high quality and are appropriately authorised for use in children, requirements for information to be available on the use of medicines in the various paediatric populations and sets up a Paediatric Committee*”. According to information on the EMA homepage, the PDCOs main role is hereby “[...] *to assess the content of paediatric*

investigation plans (PIPs) and adopt opinions on them. This includes the assessment of applications for a full or partial waiver and assessment of applications for deferrals (23).” It is, however, clearly stated that *“The PDCO is not responsible for marketing-authorisation applications for medicines for use in children. This remains within the remit of the CHMP (23).”*

If information on participation of the PDCO in a certain procedure is available, these data will be discussed in the result section below (section 3).

Further regulatory considerations should be given to the EC SmPC Guideline (24): According to the Guideline on Summary of Product Characteristics (2009), the SmPC should always include a specific sub-section on the paediatric population in the “Posology and method of administration” section 4.2. This subsection should, beside others, state if safety and efficacy have been established in a certain age group. According to the EC SmPC Guideline, section 4.2 might cross-link to further information in section 4.8, 5.1 or 5.2. The need for a cross-link to section 4.4 is, however, also imaginable.

1.1.5.2. FDA

Searching the FDA’s homepage for official FDA guidance for the development of contraceptives, no comprehensive overall guidance comparable to the European guideline was found.

However, some information on the regulatory view of the FDA can be found, e.g. as part of published information about a general meeting on contraceptives held in 2007. As part of this information, the Advisory Committee Briefing Document (25) and the protocol of the general meeting on contraceptives held by the Division of Reproductive and Urological Products in 2006 (17) have been linked to the FDA’s homepage.

According to the final summary minutes and the briefing document, topics discussed were, beside others, clinical trial design, contraceptive efficacy and risk/benefit assessment, cycle control (unscheduled bleeding and spotting), translation of clinical trial findings into the “real world”, extended dosing regimens, phase 4 commitments and the role and impact of labelling. These issues were discussed for oral and non-oral hormonal contraceptives, implantable and injectable hormonal contraceptives were not discussed, however.

Comparable to information found in the European ChMP contraceptive guideline, issues specific to the adolescent population were only addressed on the side. Some points discussed would, however, be regarded to be also related to the topic of this thesis and therefore noteworthy.

The committee agreed that in- and exclusion criteria defined for clinical studies should be *“more reflective of real world prescribing”*. The possibility to cover this aspect by subgroup

analysis was also discussed. Taking studies performed in the non-US population as an example, it was the general opinion of the committee that “*cultural and physical attributes in foreign population*” would render results “*less applicable*”. Named examples were differences in BMI and “*extremes of age*”. The obvious conclusion that the need for studies in a population closer to the “real world population” should also include studies in adolescents is then covered in the subsection on “*translation of clinical trial findings into the real world*” where the committee’s recommendation to expand “*entry criteria to include adolescents [...]*” is quoted (17).

The value of acceptability in terms of the bleeding pattern was discussed and the committee stated that as long as safety and efficacy was adequately shown, patients and treating physicians should determine on acceptability on their own. Differences in bleeding patterns between the adolescent and adult population would therefore only need to be investigated for informative purpose, as long as not related to any safety issue (e.g. blood-loss-related anaemia). Information relevant to patients and clinicians must in all cases be provided in the labelling to enable an informed decision.

The committee advocated for a product labelling including information on pregnancy rates and safety data for specific subgroups. This could reasonably be expected to also concern the adolescent population. As discussed in the results section below, information regarding clinical data in the paediatric population where rarely found in the US American Drug Summaries for contraceptives.

It was further stated that also Phase IV studies could be suitable to investigate effectiveness in subpopulations, if adequately, prospectively planned and investigating a representative population. Such an approach could allow applicants to further investigate the marketed medicinal product and acquire data on “missing information” in the adolescent population as part of a post-marketing commitment. There is also a FDA guidance already issued in 2004 about “*Labelling for Combined Oral Contraceptives*” (26) where a very concise subsection on “paediatric use” states that “*safety and efficacy are expected to be the same for post pubertal adolescents and adult women. OCs are not indicated before menarche.*”

Beyond that, a guidance published more than 20 years ago, on development of vaginal contraceptive drugs (27) was found. This historical document stated that the FDA expected more than one clinical study with at least 200 women (in total) covering 12 months of use for any product with a new “*active ingredient*”. The patient population to be investigated should have been between the ages of 18-35. No further information with regard to the adolescent population was given, however, this document must be regarded as outdated and so needs no further discussion.

1.1.6. Availability of pre-clinical models

Not all the theoretically discussed differences might be of clinical relevance and a vulnerable population should not be unnecessarily involved in early clinical studies, especially not if pre-clinical tests could be a substitution. However, at least the key issues of special relevance in the adolescent population discussed in section 1.1.4 above seem rather not investigable in pre-clinical models: Potential behavioural differences, e.g. compliance issues related to acceptability of the bleeding pattern or anatomical differences, leading to e.g. a possibly increased discomfort in wearing an intravaginal ring or to a potential higher expulsion rate of IUDs could clearly not be assessed in a pre-clinical model. It can also be assumed that no pre-clinical models are available that could predict possible differences in adult women vs. adolescent girls in terms of the bleeding pattern and its tolerability. Differences in PK parameters as found for Zoely (28) in adolescent girls (compared to adult women) cannot be investigated in a non-clinical model.

As discussed in detail in section 4, effects on bone metabolism can be associated to the suppression of the ovarian activity and endogenous E2 production (29) (30) (31). The exact degree of suppression of ovarian activity is, however, also a parameter of interest and this can only be investigated in clinical trials.

The active substance itself could, however, also effect developing organ systems like the skeletal system and this is obviously something which can be investigated in animal models. As an example, the PAR for Yasminelle (32) reports on non-clinical pharmacological studies and states that *“in rats, no effect of drospirenone was found on hormone-deficiency induced trabecular bone loss or on the bone protective effect of 17 β -oestradiol”*. The EMA Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (33) provides further information on the need for studies in juvenile animals. It states that (underlined by the author) *“standard non-clinical studies using adult animals, or safety information from adult humans, cannot always adequately predict these differences in safety profiles for all paediatric age groups, especially effects on immature systems such as the developing brain, the pulmonary system, the kidneys, the reproductive system, the immune system, the skeletal system and the organs or tissues which play a role in the pharmacokinetics of a medicinal product.”* It is, however, also stated, that *“the predictability of the nonclinical and clinical study results in adults for the paediatric population will be the key issue for the decision on whether studies in juvenile animals are needed prior to the inclusion of paediatric participants into clinical trials. The level of the predictability of data from adults for the paediatric population is age dependent. Predictability is generally low for preterm babies, newborns and infants, and increases with increasing age, being highest for adolescents.”*

Even though considered to be relevant, a more in-depth discussion on the need and design of developmental non-clinical studies is beyond the scope of this thesis.

1.1.7. Ethical considerations with regard to trial design and conduct

As discussed in the section on possible non-clinical evaluation above, vulnerable population should not be unnecessarily involved in clinical studies. If clinical data on efficacy and safety of a new contraceptive gained in the adult population can be reasonably bridged to the adolescent population, no additional studies in this vulnerable population would be expected. Which aspects will need to be paid special attention to and would be regarded to be necessarily investigated in clinical trials in adolescent girls will be discussed in summary in the discussion section below.

Noteworthy, the German AMG requirements with regard to clinical studies in adolescents are relatively strict. Article 40, Paragraph 4 of the German drug law (Arzneimittelgesetz, AMG (34)) states as follows (unofficial translation by the “Bundesgesundheitsministerium” (35), underlined and shortened by the author):

“In respect of a clinical trial on minors, sub-sections 1 to 3 shall apply with the following proviso:

1. the medicinal product must be intended to diagnose or prevent diseases in minors and the use of the medicinal product must be indicated in accordance with medical knowledge for the purpose of diagnosing or preventing diseases in the minor. The medicinal product is indicated if its administration to minors is medically indicated,

2. clinical trials performed on adults cannot be expected to produce satisfactory test results according to medical knowledge,

3. [...]

4. the clinical trial may only be conducted if it subjects the person concerned to as little burden and other foreseeable risks as possible; both the degree of burden and the risk threshold must be defined specifically in the trial protocol and monitored constantly by the investigator,

5. [...]”

Considering the German drug law cited above and acknowledging that a medicinal product used for contraception is not used to cure an illness, clinical trials in adolescent girls would probably not be approved by the national competent authority (BfArM). This might be different in COCs that beside contraception, are also indicated for e.g. acne or dysmenorrhea. In such a case, the second subsection would apply that such studies would only be possible if “*clinical trials performed on adults cannot be expected to produce satisfactory test results according to medical knowledge*” which could probably be supported for acne and dysmenorrhea. This would, however, be needed to be justified in detail and this is out of the scope of this thesis.

Subsection 4 would be interpreted as an advice to have preliminary data on efficacy and safety in adult women to ensure that adolescent girls are not exposed to unnecessary, foreseeable risks.

The requirements for the conduct of a clinical trial on minors and therefore the approval of a clinical trial protocol seems to be different within the EU. As stated in the EPAR for the COC Zoely (36), a PK study involving adolescent girls (aged 14-17 years) has been carried out. According to the European Clinical Trial Register, the clinical trial protocol (EudraCT number 2008-002142-38) for the study “*A phase I, single center, open-label parallel group trial to compare the pharmacokinetics of NOMAC between healthy female adolescents (aged 14-17 years) and healthy female adults (aged 18-50 years).*” was approved in Great Britain (37).

Outside the EU, studies in adolescents have e.g. also been conducted in the USA, as reported in the PAR of Seasonique (38).

A detailed comparison of the different legal requirements for the conduct of clinical studies for contraceptives in adolescent girls is beyond the scope of this thesis.

1.2. Objective of the current work

As discussed above, contraceptives are frequently used in a considerable subset of the very young, female adolescent population. One of the underlying question of this thesis is if clinical studies performed in adult women can cover all aspects related to safety and efficacy in the paediatric population of postmenarcheal adolescent girls or if additional studies conducted in postmenarcheal adolescent girls would also be needed. Beside possible differences in their physiological and anatomical properties there might be further aspects which need to be considered when investigating the suitability of a new hormonal contraceptive for its use in the adolescent population. The EMA Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (39) states that (underlined by the author) “*when a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, [...] extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in [...] pediatric patients [...], together with safety studies, may provide adequate information for use [...]. [...] A PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies*”. It is further stated that “*Because developing systems may respond differently from matured adult organs, some adverse events and drug interactions that occur in pediatric patients may not be identified in adult studies*”. Concerning the paediatric population between “*12 to 16-18 years*”, it is stated that in a “*period of sexual maturation*”, “*medicinal products may interfere with the actions of sex hormones and impede development*”. One of the conclusions of this guideline is that “*long-*

term studies or surveillance data [...] may be needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.”

In line with the FDA discussion on the need for clinical studies “*more reflective of real world prescribing*” (17), the following brief and very basic considerations should also be linked to the objectives of this thesis:

In general, one would expect that efficacy and safety of a medicinal product would have to be investigated in a population as close as reasonably possible to the population that will use the medicinal product once it is authorised. This would improve the so called “external validity” of the clinical study results. To a certain degree, there will, however, always be differences between the investigated population and the subjects treated in the “real world”. One of the main reasons for that is that clinical studies have to be designed to show a high degree of “internal validity” if the results shall be kept “interpretable” and reach statistical significance in a reasonable (and affordable) sample size and time frame. Random differences between patients treated in different treatment arms shall be minimized and e.g. administration and monitoring procedures need to be highly regulated in a Clinical Study Protocol. This is necessary to – ideally - investigate differences caused by the different interventions (here: medicinal products) and not by any other random factor which could differ between the treatment arms. The requirements on “internal-” as well as “external validity” will sometimes be diametrically opposed. It should be emphasized, that besides the need to cover efficacy and safety aspects in well controlled clinical studies, also (non-interventional) clinical studies with a higher “external validity” and closer to the “real world” in adolescent girls seems to be required.

The current work will focus on hormonal contraceptives. Other contraceptive options like e.g. copper IUDs or barrier methods will only be briefly considered. Based on some representative samples, it will be evaluated if clinical data on efficacy and safety in postmenarcheal adolescent girls have been provided and assessed during MAAs and/or later in the life-cycle. For this reason, first of all the information provided in the SmPC of different contraceptives will be checked for relevant information on the status of clinical studies performed in the paediatric population. As already mentioned in section 1.5.1 above, according to the Guideline on Summary of Product Characteristics (24), the SmPC should always include a specific subsection on the paediatric population in the “posology and method of administration” section 4.2.

It should be highlighted that the thesis will focus on medicinal products registered in Germany and/or Europe, respectively. Products authorised in the USA will only be briefly discussed based on the official Prescribing Information (40) and/or the Drug Summary found in the online version of the Physician’s Desk Reference (PDR) (41).

If Public Assessment Reports (PARs) are available, the question in focus will be if potential issues in the adolescent population have been discussed and if any potential need for further investigation in clinical trials has been addressed. Special obligations in the PIP or RMP to further investigate the use in postmenarcheal adolescent girls, e.g. in post-marketing studies after authorisation, will also be considered.

In summary, within this thesis, it shall be discussed if there could be a general need to modify the current regulatory praxis for contraceptives to better cover aspects with special or exclusive relevance for adolescent girls. Of course, it will be beyond the means of this thesis to investigate all authorised contraceptives. Therefore it will focus on few examples, for which data were publicly available. It is furthermore acknowledged that the discussed examples are not exhaustive and that the provided discussion is rather focused on calling attention to an area which should be paid more attention to.

2. Methods and data acquisition

2.1. Data acquisition

The author used mainly PubMed and Google Scholar to find relevant publications. All cited publications are publicly available, some, however, are liable to cost money.

Product information were either retrieved from the federal German website PharmNet.Bund (42), the Heads of Medicines Agencies (HMA) Mutual Recognition Index (MRI) (43) or the EMA homepage (44).

PARs of DCPs or European Public Assessment Reports (EPARs) of CPs, respectively, were either retrieved from the HMA MR Index (24) or the EMA homepage (25).

Further homepages of national competent authorities (NCAs, e.g. BfArM, AGES, Swissmedic, MHRA and FDA) and medical scientific societies (e.g. AWMF, DGGG, AAP) were searched for current product information, applicable regulatory guidance and clinical treatment recommendations.

2.2. Methods

No systematic review process was pre-defined. Search terms or combination of search terms used in PubMed or Google Scholar were e.g.: “*contraception, hormonal contraception, oral contraception, COC, POP, CHC, postmenarcheal, adolescent, paediatric, adverse event, bleeding pattern, tolerability, bone marrow density, peak bone mass, bone metabolism, guidance, guideline, eligibility criteria...*”. For scientific publications of possible relevance, abstracts were read and publications were then chosen by the author’s preference. A special focus was put on recent reviews, however, also older publication were taken into account if they seemed to contain relevant information. If results of clinical trials were assessed for adequacy, results from RCTs were preferred. However, data from RCTs investigating hormonal contraceptives in adolescents were found to be rarely published. Selected publications were read in full length and referenced publications therein were also considered for further reading.

Similar search terms were used for a Google research which retrieved German Publications in medical journals like “Der Gynäkologe”, “Pharmazeutische Zeitung” or “Arznei-Telegramm”.

Research in PharmNet.Bund often used advanced search. For example, if the search term was an ATC-code, output of the results was then restricted to marketed medicinal products, licensed by the BfArM (not PEI) and excluding parallel imports (search “und” “Parallelimport-Code” = “V”). If an English Version of the SmPC was available at www.mhra.gov.uk, after checking for coherence with the respective German Fachinformation, the English translations found in the UK SmPC were cited in this thesis.

Further, online versions of the “Rote Liste”, “Gelbe Liste” and “Fachinfo-Service” were also used.

US-American versions of some of the product information were searched on the homepage of the U.S. National library of medicine. For the so called physicians desk references, the search function of the website www.PDR.net was used.

To search for available PARs in the MR Index (43), e.g. the following search strategies were used for DCPs:

Search for “*Hormonal Contraceptives for Systemic Use*”:

- excludes “*Application Type Level 3*” is “*Generic*”
and
- includes “*Attached document*” of type “*PAR*”
and
- includes “*ATC-Code (catalogue)*” is “*G03 – Hormonal Contraceptives for Systemic Use*”

Only two PARs were retrieved: *Noreleva 1.5 mg*, what is an emergency contraceptive and therefore out of the scope of this thesis and *Qlaira*, a CHC containing DNG and E2.

An additional search strategy was used:

- excludes “*Application Type Level 1*” is “*Abridged*”
and
- includes “*Attached document*” of type “*PAR*”
and
- includes “*Active Substance (catalogue)*” is “*ethinylestradiol*”

PARs for *Yasmin*, *Yasminelle*, *Yaz 24+4*, and other OC containing EE and DRSP were found.

Interestingly, a search for “ethinylestradiol” (one word) and “ethinyl estradiol” (two words), both listed in the search term catalogue, retrieved different results. Some of the results using the filter “*Abridged*” for “*Application Type Level 1*” listed also generic applications. Taken together, the search function in the MR Index seems to have room for improvement. Using different strategies, in addition PARs for Seasonique (COC with EE and LNG) and Apleek (transdermal patch with EE and gestodene) were found and considered for further reading.

To search for EPARs, the “*Advanced Search*” (45) function on the EMA homepage was used. “*Hormonal Contraceptives for Systemic Use*” where than searched for as follows:

- the tab “*Keyword search*” was chosen in the “*Advanced Search*” mode, the keyword “*contraception*” was entered and the category “*Therapeutic indication*” was selected.

As a result, there were four products listed. For one of these, the application was withdrawn and another one was an emergency contraceptive. Finally, the EPARs for EVRA (transdermal patch with estradiol and NGMN) and Zoely (COC with estradiol and norgestrel acetate) were considered for further evaluation.

Information on RMP and PIP assessment were found in the (E)PARs or by a google search on the homepages of the EMA, HMA or national competent authorities. The EMA homepage also allows to search separately for “*Opinions and decisions on paediatric investigation plans*” via an adapted search mask (46).

3. Results

3.1. Hormonal contraceptives

3.1.1. Combined oral contraceptives (COCs)

According to the "Pillenreport 2015" (5), among the most frequently sold OCs in Germany in 2015 and chosen by the author as representatives for the most common combinations of an estrogen and a progestogen (progestin), there were Maxim (EE + dienogest (DNG)), Lamuna (EE + DSG), Belara (EE + chlormadinone (CMA)), Minisiston (EE + LNG) and Yasminelle (EE + DSP).

As representatives for a COC with estradiol instead of EE, Zoely (estradiol (E2) + nomegestrol (NMG)) and Qlaira (estradiol (E2) + DNG, not listed in the "Pillenreport 2015") should be mentioned here.

3.1.1.1. Information concerning the adolescent population found in the PI

As stated in the EC SmPC Guideline (24) and discussed in section 1.1.5.1, the SmPC should always at least include a specific sub-section on the paediatric population in the "Posology and method of administration" section 4.2.

The following table gives a quick overview on information with regard to the paediatric population found in the current SmPCs or "Fachinformationen" for nationally authorised products, respectively, of representative COCs.

Table 5: Sections with focus on the "paediatric population" in current SmPCs of representative COCs

Active ingredients	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
EE+ DNG	Maxim (04/2016) (47)	Section 4.2: „Kinder und Jugendliche: Maxim ist nur nach der Menarche indiziert.“ Children and adolescents: Maxim is only indicated after the menarche.
EE + DSG	Lamuna 30 (04/2016) (48)	Section 4.2: „The safety and efficacy of [...] in adolescents below 18 years has not yet been established. No data are available“ Section 5.1: " <u>Paediatric population</u> No clinical data on efficacy and safety are available in adolescents below 18 years."

Active ingredients	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
EE + CMA	Belara (05/2016) (49)	No distinct information
EE + LNG	Minisiston (09/2016) (50)	No distinct information
EE + LNG (extended-regimen)	Seasonique (10/2015) (51)	<p>Section 4.2: <i>“Paediatric population</i> <i>The efficacy and safety of Seasonique in women of reproductive age under 18 years have not been established.”</i></p> <p><i>Paediatric population</i></p> <p>Section 5.1: <i>“The European Medicines Agency has waived the obligation to submit the results of studies with Seasonique in all subsets of the paediatric population in contraception (see section 4.2 for information on paediatric use).”</i></p>
EE + DSP	Yasminelle (07/2015) (52)	No distinct information
E2 + NMG	Zoely (05/2016) (28)	<p>Section 4.4: <i>“<u>Paediatric population</u></i> <i>It is unknown whether the amount of estradiol in Zoely is sufficient to maintain adequate levels of estradiol in adolescents, especially for bone mass accrual (see section 5.2).”</i></p> <p>Section 5.1: <i>“<u>Paediatric population</u></i> <i>No data on efficacy and safety are available in adolescents below 18 years. Available pharmacokinetic data are described in section 5.2.”</i></p> <p>Section 5.2: <i>“<u>Paediatric population</u></i> <i>The pharmacokinetics of nomegestrol acetate (primary objective) after single oral dosing of Zoely in healthy postmenarcheal female adolescents and adult subjects were similar. However, after single oral dosing, for the estradiol component (secondary objective), the exposure was 36 % lower in adolescents versus adult subjects. The clinical relevance of this result is unknown.”</i></p>

Active ingredients	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
E2 + DNG	Qlaira (11/2015) (53)	Section 4.2: " <i>Children and adolescents</i> <i>No data available for use in adolescents below 18 years.</i> "

The database for this table were the exemplary current SmPCs or "Fachinformationen", respectively, dated as indicated in the table. Sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 were checked for any information specially related to the use in the paediatric population, here postmenarcheal adolescent girls.

Representative samples of US American Prescribing Information found on the homepage of the US National Library of Medicine (40) were checked for corresponding information. Not all of the prescribing information provided had a subsection "pediatric use" as recommended in the FDA publication about "*Labelling for Combined Oral Contraceptives*" (2004) (26). For Yasmin, in line with the FDA publication, this subsection stated as follows: "*Safety and efficacy of Yasmin has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated*" (54). The same wording was found in the prescribing information for Natazia and Seasonique.

In addition, samples of US American Drug Summaries found in the online version of the Physician's Desk Reference (PDR) (41) were also checked. The subsection "*Pediatric Dosage & Indication*" states "*not indicated for use premenarche; refer to adult dosing*" for Velivet, a COC containing EE and DSG (55). No further warnings or information of particular interest in adolescent girls were found. A similar wording and absence of further information focused on the paediatric population was found for other COCs, including combinations of EE + DRSP (Yasmin) (56), EE + LNG (Altavera) (57), EE + LNG (Seasonique, extended regimen) (58) and E2 + DNG (Natazia) (59).

3.1.1.2. Regulatory considerations

For the EU, according to the SmPCs cited above, there are various COCs marketed for which there are either no data available for use in children below the age of 18 years, or, where at least no further information on clinical studies performed in children below the age of 18 can be found. The absence of such information or the chosen wording in most of the SmPCs would not be interpreted to indicate that an indication in women below 18 years is not granted. An exemption might be the wording found in the SmPC for Lamuna and Seasonique, which states (in similar wording) that the safety and efficacy in adolescent girls has not been established (48; 51).

For some of the COCs listed above, PARs are publicly available, e.g. for the centrally authorised COC Zoely on the EMA homepage (36) or the decentralised authorised COCs Qlaira (60), Yasminelle (32) and Seasonique (38) at the MRI (43).

The EPAR for Zoely might be the one of the more informative publications to understand how the data available for the adolescent population at the time of the MAA for one of the newer COCs have been discussed and assessed by the ChMP.

According to the EPAR for Zoely (36), the applicant applied for the indication “*Oral contraception. Zoely 2.5mg/1.5mg, film-coated tablet is indicated in fertile women including post-menarcheal adolescents from the age of 12 years.*” However, the approved indication by the CHMP was finally: “*Oral contraception*”. The following is a verbatim quote from the EPAR (36) underlined by the author:

“The CHMP therefore agreed that no extrapolation of efficacy and safety results as found in the phase III clinical program for adults can be made to the post-menarcheal adolescent population. Indeed, lower E2 levels were observed in the adolescent population aged 14-17 years compared to an adult population. It seems difficult in that context to also extrapolate pharmacokinetic, efficacy and safety data observed in the 14-17 years to the 12-13 years age group. Thus, the applicant’ proposal to only accept the following indication “Oral contraception” (Section 4.1.) and deleting all reference to “fertile women including post menarcheal adolescents from the age of 12 years” has been endorsed by the CHMP. Information regarding the paediatric population in the respective sections of the SmPC has been agreed on by the SmPC [should probably state “ChMP” not “SmPC”].”

The Pharmacovigilance section states in the subsection on the RMP that “safety in postmenarcheal adolescents” is an “Important missing information” and the “proposed risk minimisation activities” to deal with this risk are routine activities and the inclusion of a statement in the SmPC that “safety in adolescents below 18 years has not been established”. No specific post authorisation safety studies (PASS), e.g. to further investigate potential detrimental effects on bone metabolism or to tolerability in terms of bleeding pattern and adverse events in adolescents have been imposed.

In the benefit risk discussion the EPAR states in summary “[..] *no extrapolation of efficacy and safety results as found in the phase III clinical program for adults can be made to the post-menarcheal adolescent population. Thus, an extension of use in this age class cannot be endorsed by the CHMP [...].*”

As indicted in the table above, information on the amount of efficacy and safety data in the post-menarcheal adolescent population can be found in section 5.1 and 5.2, a warning with regard to potential detrimental effects on bone mass accrual can be found in section 4.4.

The German journal *Arznei-Telegramm* reported about Zoely in 2012 (61) and the authors expressed their concerns that the indication was not explicitly restricted to adult women of at least 18 years of age and that information on the lack of data in the post-menarcheal adolescent population were only covered in the later sections of the authorised SmPC.

Noteworthy, the Swiss NCA Swissmedic authorised Zoely for the use in adults only. The current Swiss “Fachinformation” for Zoely states the indication “*Hormonale Kontrazeption bei Frauen ab 18 Jahren*. [hormonal contraception in women of at least 18 years]” which is justified by the limited amount of safety data derived from clinical studies in adolescents: “[...] *Zur Anwendung von Zoely bei Jugendlichen unter 18 Jahren liegen nur limitierte Daten vor. Bis zum Vorliegen weiterer Sicherheitsdaten ist Zoely für die Anwendung bei Jugendlichen nicht zugelassen (siehe «Warnhinweise und Vorsichtsmassnahmen»)* (62)“.

According to information found in the EPAR, the PK study in adolescents was part of an agreed PIP that was completed at the time of the ChMP opinion. It is further stated that a product specific waiver and deferral was granted and that a positive opinion on compliance was issued by the PDCO. However, a publicly available PIP AR for this procedure to gain more detailed insight in the rationale for the chosen design of the clinical trials in adolescent girls could not be retrieved.

The PAR for Qlaira (60) states that “*no paediatric development programme has been submitted*” which confirms the information found in the SmPC that no clinical studies in the paediatric population have been performed to support the MAA. Efficacy or safety in adolescent girls have not been specially focused on in the benefit-risk discussion of the PAR. Potential effects on E2 concentrations and subsequently detrimental effects on bone metabolism and achieving an adequate peak bone mass have also not been further discussed. However, as part of the RMP, there were post-approval commitments to be made by the applicant during the procedure. One post-approval commitment was to conduct a large comparative post-marketing safety surveillance study to assess the VTE risk of Qlaira compared to other COCs in a non-selected target population (INAS-EV) and a preferential prescribing monitoring program (observational study). The Applicant had to explicitly commit to also include women below the age of 18 years in this clinical study. The wording in section 4.2 of the SmPC “Children and adolescents: No data available for use in adolescents below 18 years” would not be interpreted to indicate that an indication in women below 18 years is not granted. The PDCO opinion on the submitted PIP and the granting of a waiver for Qlaira (63) can be found on the EMA homepage. The PDCO grants a waiver for boys and girls from birth to menarche “*on the grounds that the specific medicinal product does not represent a significant therapeutic benefit*” which is self-evident. However, for “*girls from menarche to less than 18 years*”, a waiver was also granted. This was justified “*on the grounds that the specific*

medicinal product does not represent a significant therapeutic benefit". A closer look on the role of the PDCO will be taken in the discussion section below.

The PAR for Yasminelle (32) indicates that no studies in adolescents below 18 years of age have been performed, which is somewhat in line with the absence of information found in the SmPC. Noteworthy, during the Mutual Recognition Procedure for Yasminelle, the application was referred to the CMDh and the informative texts were extensively discussed. From a historical point of view, this referral was a huge step towards more harmonised product information for OCs, as many sections are of similar content in most of the SmPCs (Posology, missed pill advice, ...) and warnings are often related to class effects. The final wording chosen for the SmPC and PL of Yasminelle after the referral was generally acceptable in most of the Member States from then onwards. However, harmonised sections with regard to information on the "paediatric population" were (unfortunately) out of the scope of this referral. The EMA homepage provides information on a PDCO Opinion on "YAZ and associated names (EMA-000148-PIP01-07)" dated February 2009. A waiver for all age classes was established and the PIP refused. The stated reasons did not comment on potential safety issues, beside others, the waiver was granted on grounds "*that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients*".

According to the PAR for Seasonique (38), in this application, the PDCO was involved as the company submitted an application for a product-specific waiver pursuant to Article 13 of Regulation (EC) No 191/2006 as amended. As a result, a product specific waiver was granted for all subsets of the paediatric population by the PDCO. The stated reason cited in the PAR was "*the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s) and on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients*".

Although not demanded by the PDCO, two studies in adolescent women were performed: a phase II study to evaluate the effect on pelvic pain and another phase II study to evaluate the effect on bone mineral density. The later, study DR-105-202, was a "*Multi-centre, open-label, randomized, controlled study to determine the effects on bone mineral density (BMD) in healthy adolescent females using Seasonique or a 28-day OC (Lessina) compared with healthy adolescent females not using hormonal contraception (control group)*". The study duration was 12 months and the primary endpoint was "*Mean percent change in lumbar spine BMD measured via DXA over a 12-month period*". The endpoint assessed in the second clinical study in adolescent girls, a randomized, multicentre, two-arm, double-blind, placebo-controlled study, was "*change in subject-reported severity of menstrual-related pelvic pain as recorded in the daily diary, using a 4-point grading scale*". The study duration was "*13 weeks mandatory*".

plus an optional 13-week blinded extension". Both studies were conducted in the USA (see section 1.1.7 for possible legal issues for clinical studies on contraceptive use in adolescents). Noteworthy, even though clinical studies in adolescent girls were conducted, it was assessed that these studies were not adequate to establish efficacy and safety in "*women of reproductive age under 18 years*". This is - in content - also the information stated in section 4.2 of the current SmPC. The RMP section of the PAR emphasizes that "*Use in women under 18 years of age*" is one of the "*Missing information*", further, the clinical study on potential detrimental effects was not taken into account because of its explorative design (phase II study). Decreased bone density is stated in the RMP as "*important potential risk*", even though the assessment summarises the results of the respective clinical study as follows: "*Overall, the data on bone mineral density in adolescent using Seasonique are reassuring.*" With regard to the efficacy to improve dysmenorrhea in adolescent women, according to the assessment, "*the results of this phase II exploratory study are only seen as supportive, as no active control group was included*". Noteworthy, dysmenorrhea is none of the approved indications and Seasonique is only indicated for oral contraception.

3.1.1.3. Regulatory status in view of the current state of medical knowledge

In the EU, the current state of scientific knowledge regarding efficacy and safety of combined COCs use in postmenarcheal adolescent girls seems to be overall adequately covered in the informative texts. Information concerning the amount of data available on the use in the adolescent population and uncertainties of potential effects on BMD could, however, be more precise and apparent (see section 3.1.1.1). According to eligibility criteria published by the WHO (7), COCs are assessed to be "category I" in adolescents. As discussed in detail in section 1.1.4, the high contraceptive efficacy and the good compliance often coming along with a favourable bleeding pattern are endorsed. Study results for COCs using E2 instead of EE like Zoely or introduction of extended cycle regimens as for Seasonique showed that potential detrimental effects on bone metabolism need to be further investigated. Few is known about the effects of older COCs and reliable results from controlled RCT covering prolonged periods are sparse. Most data come from retrospective case-control and observational studies. Limitations are foreseeable, especially as the clinical outcome of interest is rather a potential increase in fracture rates than measured changes in surrogate parameters like BMD or biochemical markers of bone resorption. This issue will be discussed in the light of possible suppressive effects on endogenous E2 plasma concentrations, which have also been shown for other hormonal contraceptives in the discussion section below. In conclusion, however, it should be noted that the limited data currently available would rather question clinically relevant effects on bone metabolism and peak bone mass accrual, at least for COCs containing 30 µg EE.

3.1.2. Progestogen-only pills (POPs)

According to an online research, beside others in the federal online drug information system “PharmNet.Bund”, Progestogen-only pills (POPs) in Germany contain either the progestogen DSG or LNG (42). One representative example for each active substance was chosen by the author: For DSG containing POPs, on the basis of availability of a current English version of informative texts at the HMA MR Index, Delamomie (generic to Cerazette (DSG)). For LNG containing POPs, Microlut. However, no English informative texts were available for the later.

In contrast to POPs containing LNG which work mainly by influencing the cervical mucus and the endometrium, similar to COCs, POPs containing the progestogen DSG work primarily by inhibition of ovulation. As stated in the “Fachinformation” of Microlut (64) POPs containing LNG need to be taken every 24 h, as regularly as possible. The time window for a compliant intake is only +/-3 hours, if contraceptive efficacy should not be endangered. For POPs containing DSG, according to the SmPC of Delamomie (65) “*contraceptive protection may be reduced if more than 36 hours have elapsed between two tablets.*” In consequence, the use of DSG containing POPs may be more appropriate for adolescents if compliance issues with the need for regular intake can be foreseen.

3.1.2.1. Information concerning the adolescent population found in the PI

The following information with focus on the paediatric population can be found in the current SmPCs for Delamonie and Microlut:

Table 6: Sections with focus on the “paediatric population“ in current SmPCs of representative POPs

Active ingredient	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
LNG	Microlut (05/2016) (64)	Section 4.2: „ <i>Kinder und Jugendliche: Vor der Menarche gibt es keine relevante Indikation für Microlut.</i> “ Children and adolescents: There is no relevant indication for Microlut before the menarche.
DSG	Delamonie (05/2016) (65)	Section 4.2: „ <i>The safety and efficacy of {Nationally completed name} in adolescents below 18 years has not been established. No data are available</i> “ Section 4.4: “ <i>Treatment with {Nationally completed name} leads to decreased estradiol serum levels, to a level corresponding with the early follicular phase. It is as yet unknown whether the decrease has any clinically relevant effect on bone mineral density.</i> ” [related to peak bone mass accrual in adolescents] Section 5.1: “ <i>Paediatric population</i> <i>No clinical data on efficacy and safety are available in adolescents below 18 years.</i> ”

The database for this table were the exemplary current SmPCs or “Fachinformationen”, respectively, dated as indicated in the table. Sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 were checked for any information specially related to the use in the paediatric population, here postmenarcheal adolescent girls.

According to UpToDate, only one POP formulation, [Ortho] Micronor (NET) is marketed in the USA (66). No other POPs were identified by further research in the online version of the PDR (41). The prescribing information contains the recommended “standard wording” (see section 1.1.5.2) also found for COCs discussed in the subsections above, namely that “*safety and efficacy [...] have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents [...]*” (67).

The subsection “*Pediatric Dosage & Indication*” of the Drug Summary of Ortho Micronor (68) states “*not indicated for use premenarche; refer to adult dosing*”. No further warnings or information of particular interest in adolescent girls were found.

3.1.2.2. Regulatory considerations

According to the SmPCs cited above, for the POPs marketed in the EU, there are either no data available for use in children below the age of 18 (Delamonie) or at least no further information on clinical studies performed in children below the age of 18 can be found (Microlut). The absence of such information or the chosen wording in the SmPCs would not be interpreted to indicate that an indication in women below 18 years is not granted. The SmPC for Delamonie states that “*The safety and efficacy of {Nationally completed name} in adolescents below 18 years has not been established. No data are available*” and contains a warning on possible negative effects on bone mineral density. This could be interpreted as information for the treating physician to perform a more thorough individual benefit-risk assessment in postmenarcheal adolescent girls, however, the information would be regarded as rather unobtrusive. Unfortunately, no PAR or EPAR could be retrieved and it is therefore not known if any efficacy or safety issues of special relevance for adolescent girls have been discussed during the MAA assessment. In the MR Index, only some few administrative information on a withdrawn application for a POP (ATC-code G03AC is stated) containing 4 mg DRSP can be found (DE/H/4153/001). On the EMA homepage, a PDCO opinion dated May 2016 on the modification of an agreed PIP for a DRSP containing POP issued in May 2014 can be found (69). In this PDCO opinion, a PIP in girls “*from menarche to less than 18 years of age*” is agreed to. The required study is named “*Open-label, 6-month study to assess bleeding pattern, safety, tolerability of drospirenone in adolescent girls requiring oral contraception*”. Even though no POP containing DRSP is currently marketed, the cited PDCO opinion would be interpreted to show that the PDCO is currently also focusing on contraception in adolescent girls and applicants need to be aware that OCs will not *per se* get a waiver, like it was decided earlier e.g. for Yaz or Qlaira (both 2009).

3.1.2.3. Regulatory status in view of the current state of medical knowledge

As discussed in section 1.1.4, POPs should be preferably prescribed for contraception in adolescents with cardiovascular risk factors that are not eligible for COCs. This is due to the often unfavourable bleeding pattern which might result in non-compliance or early discontinuation. In a publication by Merki-Feld et al. (12) it is discussed that a less favourable bleeding pattern with e.g. breakthrough-bleeding, breakthrough-spotting or amenorrhea is often less well accepted in young women. For LNG containing POPs, the strict dosing regimen (every 24h +/- 3 h) has also to be taken into account. Noteworthy, non-compliance to the strict posology requirements could lead to a higher rate of user failures. Depending on their ability to suppress endogenous E2 production, POPs could also negatively influence bone metabolism. Curtis et al. published the review “*Progestogen-only contraception and bone mineral density: a systematic review*” (70) in 2006 which mainly discussed progestogen only

methods in dosage forms of depot injections containing MPA. POPs are, however, also discussed. The review concludes that *“Although evidence is limited, women using other forms of progestogen-only contraceptives [others than DMPA] do not appear to have lower BMD than nonusers.”*

According to eligibility criteria published by the WHO (7), POPs are assessed to be category I in adolescents.

3.1.3. Depot injections

In Germany, according to PharmNet.Bund (42) and excluding parallel imports, there are currently 2 depot injections indicated for contraception containing MPA registered. These are Depo-Clinovir and SAYANA 104 mg/0,65 ml Injektionssuspension. Another registered depot contraception is Noristerat 200 mg Injektionslösung containing NET as active ingredient.

3.1.3.1. Information concerning the adolescent population found in the PI

Table 7: Sections with focus on the “paediatric population“ in current SmPCs of representative Depot-Injections

Active ingredient	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
MPA	SAYANA (07/2016) (71)	<p>Section 4.1 (*): „[...] <i>Use in Adolescents (12-18 years): In adolescents, use of SAYANA is only indicated when other contraceptive methods are considered unsuitable or unacceptable, due to unknown long-term effects of bone loss associated with SAYANA during the critical period of bone accretion (see section 4.4.).</i></p> <p><i>SAYANA has not been studied in women under the age of 18 years but data is available for intramuscular MPA in this population.”</i></p> <p>Section 4.2: “[...] <i>Paediatric: SAYANA is not indicated before menarche [...]. Data in adolescent females (12-18 years) is available for IM administration of MPA [...]. Other than concerns about loss of BMD, the safety and effectiveness of SAYANA is expected to be the same for adolescents after menarche and adult females.”</i></p> <p>Section 4.4: Elaborately information about possible detrimental effects on bone metabolism and peak bone mass accrual justifying the second line indication stated in section 4.1, e.g.: “[...] <i>This loss of BMD is particular concern during</i></p>

Active ingredient	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
		<p><i>adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of SAYANA by younger women will reduce peak bone mass and increase the risk for fracture in later life. [...]</i></p> <p>Section 5.1: Subsection representing the results of a clinical study investigating the effects of MPA on the BMD in women between 12-18 years of age.</p>
MPA	Depo-Clinovir (08/2016) (72)	<p>Section 4.1 (**): This section states that Depo-Clinovir is only indicated for long term contraception (3 months) in women, when other contraceptive methods are considered unsuitable, which is further explained and linked to the potential use in adolescents in the following sections.</p> <p>Section 4.2: This section states that intramuscular administration of MPA before the menarche is contraindicated. It is further stated that results of clinical studies in adolescent girls (12-18 years) indicate that, with the exemption of possible detrimental effects on BMD, efficacy and safety of intramuscular administration of MPA is comparable in adult and postmenarcheal adolescent girls.</p> <p>Section 4.4.: Elaborately information about possible detrimental effects on bone metabolism and peak bone mass accrual justifying the second line indication stated in section 4.1.</p> <p>Section 5.1.: Subsection representing the results of a clinical study investigating the effects of MPA on the BMD in women between 12-18 years of age.</p>
NET	Noristerat (07/2014) (73)	<p>** Section 4.1: This section states that Noristerat is only indicated for long term contraception (3 months) in women, when other contraceptive methods are considered to be unsuitable (e.g. disturbed gastro-intestinal resorption, E2 intolerance, foreseeable compliance issues).</p> <p>Section 4.2: This section states that Noristerat is indicated only after the menarche and cross-links to the warning section on bone metabolism.</p>

Active ingredient	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
		<p>Section 4.4: Elaborately information about possible detrimental effects on bone metabolism and peak bone mass accrual justifying the second line indication stated in section 4.1.</p> <p>Section 4.8: Information about possible detrimental effects on bone metabolism and a cross-link to section 4.4.</p>

The database for this table were the exemplary current SmPCs or "Fachinformationen", respectively, dated as indicated in the table. Sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 were checked for any information specially related to the use in the paediatric population, here postmenarcheal adolescent girls.

(*) For SAYANA, an English SmPC was available at www.mhra.gov.uk. After checking coherence with the German Fachinformation, the English translations found in the UK SmPC was cited.

(**) No English original translations were available, the German Fachinformation was therefore translated in content by the author

The section on "paediatric use" in the US American Prescribing Information for Depo-Provera Contraceptive Injection (74) states that "[...] *It is unknown if use of Depo-Provera CI by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.*" clearly informing the prescribing physician about potential detrimental effects on bone metabolism. This issue is also covered in further sections, e.g. the "warning/precautions" or "adverse reaction" section.

The US American Drug Summary of Depo-Provera Contraceptive Injection (74) states "*not indicated for use premenarche; refer to adult dosing*" which is the same as in the respective sections in COCs or POPs discussed above. However, very prominent in the first section of the Drug Summary there is a "boxed warning" on potential detrimental effects on bone metabolism, an aspect, which is also covered in e.g. the "warning/precautions", "adverse reaction" or "monitoring" section (74).

3.1.3.2. Regulatory considerations

The EU SmPCs cited above contain subsections with further information on paediatric use in section 4.2 of the current SmPCs. The use of MPA or NET containing depot injections is clearly labelled as later line indication and the main reason for this, namely potential detrimental effects on bone metabolism in a critical phase of peak bone mass accrual, is clearly stated.

In 2004, Pfizer had to send a "Dear Doctors Letter" to inform healthcare professionals about an important updated safety information for Depo-Provera Contraceptive Injection (75) in the USA. A black box warning with special relevance for women during adolescence or early

adulthood, which is cited in content above, had to be added. Long-term use shall be restricted only to women when other contraceptive options were judged to be inadequate, also according to the US label.

3.1.3.3. Regulatory status in view of the current state of medical knowledge

As discussed in section 1.1.3, detrimental effects on bone metabolism and peak bone mass accrual have been seen in clinical studies for DMPA. Effects on fracture rates in later life are discussed controversially. However, due to the known possible risks with regard to the loss of BMD, it is widely agreed that DMPA is only indicated if other contraceptive methods are considered unsuitable or unacceptable, e.g. in women with compliance issues. According to eligibility criteria published by the WHO (7), for the use of Depot injections “*the advantages of using the method generally outweigh the theoretical or proven risks*” (category II). The current state of scientific knowledge regarding efficacy and safety of Depot injection use in postmenarcheal adolescent girls seems to be adequately covered in the informative texts.

3.1.4. Intravaginal ring

Currently, there is only one registered product which is the NuvaRing containing EE and etonogestrel (ETG) which works comparably to COCs, with the difference that the active substances are absorbed via the vaginal mucosa (76). Local effects seem to be negligible, the SmPC states that “*Cervical and intrauterine etonogestrel levels were measured in a small number of women using NuvaRing or an oral contraceptive containing 0.150 mg desogestrel and 0.020 mg ethinylestradiol. The observed levels were comparable.*”

3.1.4.1. Information concerning the adolescent population found in the PI

The current SmPC for NuvaRing found in the HMA MR Index states the following information focusing on the paediatric population:

Section 4.1: “[...] *NuvaRing is intended for women of fertile age. The safety and efficacy have been established in women aged 18 to 40 years [...]*”

Section 4.2: “*Paediatric population: The safety and efficacy of NuvaRing in adolescents under the age of 18 have not been studied.*”

Section 5.1: “*EFFECTS ON BONE MINERAL DENSITY. The effects of NuvaRing (n=76) on bone mineral density (BMD) were studied in comparison to a non-hormonal intrauterine device (IUD) (n=31) in women over a period of two years. No adverse effects on bone mass have been observed.*”

Paediatric population: The safety and efficacy of NuvaRing in adolescents under the age of 18 have not been studied.”

Section 5.2: *“Paediatric population. The pharmacokinetics of NuvaRing in healthy postmenarcheal female adolescents under the age of 18 have not been studied”*

The NuvaRing is also marketed in the USA. The Prescribing Information states the standard information recommended by the FDA publication on labelling (26). The US American Drug Summary for NuvaRing does not contain any information about the status in respect to clinical studies performed in postmenarcheal girls below 18 years of age (77). Instead, the standardized wording *“Not indicated for use premenarche; refer to adult dosing”* can be found in the respective subsection.

3.1.4.2. Regulatory considerations

With regard to the EU, the HMA MR Index (78) provides the information that there has been a positive outcome for the initial application in the DCP NL/H/0265/001 for NuvaRing at 12. June 2001. Unfortunately, no publicly available information on the clinical data provided within the MAA in the sense of a PAR for NuvaRing have been linked here. However, the current SmPC for NuvaRing (76) clearly states that safety and efficacy of NuvaRing in adolescents under the age of 18 have not been studied and it contains a warning on possible negative effects on bone mineral density. This would be regarded adequate to inform the treating physician about possible uncertainties and possible detrimental effects on bone metabolism. It seems therefore ensured that the treating physician is aware of the need of a thorough individual benefit-risk assessment in postmenarcheal adolescent girls. At the time of the MAA for NuvaRing, the so-called “Paediatric Regulation” was not yet in force and there was no need for the applicant to submit a Paediatric Investigation Plan (PIP) (79).

3.1.4.3. Regulatory status in view of the current state of medical knowledge

Possible effects of the NuvaRing Bone on BMD have been investigated in adults in a study by Massi et al. (80). Seventy-three NuvaRing users were investigated and compared to 30 women not using hormonal contraceptive methods in a clinical study of approximately 2 years duration (26 cycles). The difference found was assessed to be clinically not relevant, however, acquisition of peak bone mass seemed to be somewhat decreased in the active group. No clinical data in adolescent girls were found in the published literature. This is in line with the AAP Technical Report which states with regard to potential effects on BMD: *“The limited investigation of bone health with the ring points to its bone neutrality, but these studies have not included adolescents younger than 18 years.”* With regard to cardio-vascular risks, it is stated that *“studies to date have yielded inconsistent results about how the risk of VTE with use of the ring compares with the risk with use of low-dose COCs”* (16). Compliance could be an issue in the adolescent population, according to information found in *“UpToDate”* (81), *“anecdotal evidence suggests that some adolescents do not feel “clean” with the vaginal ring and have the need to wash it frequently. Frequent washing decreases effectiveness and may*

cause intermittent bleeding or spotting". It is also discussed that probably some adolescents might not feel comfortable with inserting the ring in the vaginal canal, especially those not using tampons during menses. According to the author's research and in line with what is stated in the current EU SmPC, efficacy and safety as well as tolerability and acceptability of the intravaginal ring need to be further investigated in postmenarcheal adolescent girls.

The current state of scientific knowledge regarding efficacy and safety of its use in postmenarcheal adolescent girls seems, however, to be adequately covered in the EU SmPC, see subsection above. According to eligibility criteria published by the WHO (6), NuvaRing is "category I" (see section 1.1.3).

3.1.5. Transdermal contraceptive patch

Currently, there is only one registered transdermal contraceptive patch on the German market which is the EVRA 203 micrograms/24 hours + 33.9 micrograms/24 hours transdermal patch [from now on referred to as EVRA] containing EE and norelgestromin (NGMN) which works comparably to COCs, with the difference that the active substances are absorbed through the skin after the patch has been applied to "*the buttock, abdomen, upper outer arm or upper torso, in a place where it will not be rubbed by tight clothing*" according to the SmPC (82).

Another transdermal contraceptive patch called Apleek, releasing 60 µg gestodene per 24 hours and 13 µg EE per 24 h, can be found in the MRI, the positive outcome of the DCP FR/H/0547/01 was stated to be the 11.02.2014. Although Germany was one of the CMS according to the MRI, no such product is listed on e.g. "PharmNet.Bund" or "Rote-Liste online". However, as Apleek is one of the products where a PAR is available, assessment of data relevant to the adolescent population will be briefly discussed below.

3.1.5.1. Information regarding the adolescent population found in the PI

The current SmPC for EVRA found on the EMA homepage states the following information with regard to the paediatric population:

Section 4.1: "[...] *EVRA is intended for women of fertile age. The safety and efficacy has been established in women aged 18 to 45 years [...]*"

Section 4.2: "*Paediatric population: Safety and efficacy have not been established in adolescents under 18 years of age. There is no relevant use of EVRA in children and pre-menarcheal adolescents.*"

No SmPC was available at the MRI for *Apleek*. Via Google search, a SmPC was found on the homepage of the Irish NCA (83). The wording of the indication is very close to the wording of EVRA stated above.

The online version of the US American PDR states that marketing of Ortho EVRA transdermal patches has been discontinued, however, a Drug Summary for another transdermal patch called Xulane (EE + NGMN) can be found (84). The Prescribing Information states the standard information recommended by the FDA publication on labelling (26), also for the PDR's Drug Summary, standard information that the use is not indicated before menarche can be found in the subsection on "pediatric dosage & indications" and no further information or warnings, respectively, with focus on postmenarcheal adolescents are given.

3.1.5.2. Regulatory considerations

The EPAR for *EVRA* states in a subsection on "*special populations*" that "*the pharmacokinetic profile of EVRA has not been evaluated in children nor in adolescents*" (85). In the three phase III clinical studies, only healthy adult females in the range of 18-45 years have been studied (inclusion criteria).

According to the PAR on *Apleek* dated February 2014 (86), the legal basis for the MAA was Article 8(3) of Directive 2001/83/EC ("known active substance"). In a subsection on paediatrics, it is stated that "*The CMDh considered in April 2012 that Article 7 or 8 of the Paediatric Regulation is not applicable to the MAA for Apleek. Therefore, no Paediatric Investigation Plan was submitted*". It is further concluded, that, as no adolescent girls below 18 year of age were included in the clinical development programme, efficacy and safety in adolescents below 18 years of age have not been established. The section on the RMP does not list "Use in women under 18 years of age" as an "important missing information", no PASS to further investigate efficacy and safety in adolescent girls were planned. The applicant had to commit to perform a PASS to "*characterize and compare the risks of Apleek to a LNG-containing COC*". If adolescent girls will be included in this PASS was not reported.

3.1.5.3. Regulatory status in view of the current state of medical knowledge

The current state of scientific knowledge regarding efficacy and safety of transdermal contraceptive patches in postmenarcheal adolescent girls seems to be adequately covered in the informative texts in the EU. The SmPC for *EVRA* clearly states that safety and efficacy in adolescents under the age of 18 have not been studied, noteworthy, in addition to information in section 4.2 "paediatric population" also prominent in section 4.1 "indication". It seems therefore to be ensured that the treating physician is aware of the need of a thorough individual benefit-risk assessment in postmenarcheal adolescent girls. Prescribing *EVRA* to women below 18 years would be regarded as an "off-label use". Similar to *EVRA*, the information found in the SmPC of *Apleek* with regard to the paediatric population would be regarded to be adequate.

According to eligibility criteria published by the WHO (7), transdermal patches are regarded to be category I, being potentially a first choice contraceptive also in adolescent girls (see section 1.1.3).

The AAP states in their publication on contraceptives in adolescents that “*the 2012 package insert contains a black box warning citing 5 US studies (1 with statistically significant findings) that suggest a possible increased risk of VTE compared with a 20- to 35- μ g COC, with odds ratios of 1.2 to 2.2. Although these potential health risks are concerning to some adolescents, the patch remains an important contraceptive alternative that may be the best option for some adolescents, especially in comparison with the many adverse consequences of unplanned pregnancy, which include an increased risk of VTE. Nonetheless, other methods may be safer first-line choices for patients interested in extended cycling*” (16).

3.1.6. Intrauterine devices

As discussed in section 1.1.2, according to the DGGG about 6% of all women of reproductive age in Germany use hormonal IUDs. According to a research in PharmNet.Bund (42) using the ATC code G02BA03 and excluding parallel imports there are currently two licensed hormonal IUDs in Germany: Jaydess and Mirena. Both IUDs contain LNG as active ingredient.

3.1.6.1. Information concerning the adolescent population found in the PI

Table 8: Sections with focus on the “paediatric population“ in current SmPCs of representative hormonal IUDs

Active ingredient	SmPC (last update)	SmPC sections with focus on the paediatric population (postmenarcheal adolescent girls)
LNG	Jaydess (6/2016) (87)	<p>Section 4.2 (*): <i>“Use of this product before menarche is not indicated. For data on safety and efficacy in adolescents, see section 5.1”</i></p> <p>Section 4.4: <i>“[...] Because an ectopic pregnancy may impact future fertility the benefits and risks of using Jaydess should be carefully evaluated, in particular for nulliparous women. Use in nulliparous women: Jaydess is not first choice for contraception in nulliparous women as clinical experience is limited.”</i></p> <p>Section 5.1: <i>“[...] The safety profile of Jaydess observed in a study of 304 adolescents was consistent with that in the adult population. Efficacy is expected to be the same for adolescents under the age of 18 as for users 18 years and older [...]”</i></p>
LNG	Mirena (08/2016) (88)	<p>Section 4.2 (**): This section states that safety and efficacy of Mirena in adolescents below 18 years of age have not been adequately investigated and that there is no relevant indication before the menarche.</p> <p>Section 4.4.: This section states in a subsection on parity that Mirena should preferably be used in women who have already given birth. It is stated to be not first choice for contraception in young nulliparous women and should only be considered if other reliable contraceptive methods cannot be used.</p> <p>Section 5.1.: Subsection representing the results of a clinical study investigating the effects of MPA on the BMD in women between 12-18 years of age.</p>

The database for this table were the exemplary current SmPCs or “Fachinformationen”, respectively, dated as indicated in the table. Sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 were checked for any information specially related to the use in the paediatric population, here postmenarcheal adolescent girls.

(*) For Jaydess, an English SmPC was available at www.mhra.gov.uk. After checking coherence with the German Fachinformation, the English translations found in the UK SmPC was cited.

(**) No English original translations were available, the German Fachinformation was therefore translated in content by the author

Mirena is also marketed in the USA. The Prescribing Information states the standard information recommended by the FDA publication on labelling (26), stating that “Efficacy is

expected to be the same for postpubertal females [...] (89)". Noteworthy, in the Drug Summary for Mirena (90), the indication is narrowed to "rather" exclude nulliparous women, it states "*recommended for females who have had at least 1 child*". The subsection on "pediatric dosage & indications" provides the known standard wording on use only after menarche. The subsection on "patient counselling" highlights the need to inform women about "*the risk of ectopic pregnancy, including loss of fertility*".

3.1.6.2. Regulatory considerations

The PAR for Jaydess, dated December 2012, is available at the MRI (91). The PAR discussed that the applicant "*wanted to target Jaydess to nulliparous women*". This indication was, however, removed during the discussion, according to the PAR, due to the limited data in this special population. Changes in BMD were assessed in a subset of patients, according to the AR "*no difference in bone mineral density was observed during LCS12 treatment*". However, the studies investigated BMD changes in adults and not during a potentially more vulnerable time of peak bone mass accrual in adolescents. Bayer submitted a PIP to the PDCO, the PDCO Opinion is publicly available on the EMA homepage (92). It is obvious that a waiver was acceptable for "*Boys from birth to less than 18 years of age*" and "*Girls from birth to age of menarche*" as "*the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s)*." For "*Girls from age of menarche to less than 18 years of age*", a deferral was accepted and a study investigating the "*low dose LNG IUS*" (namely Jaydess) had to be completed by September 2013. Bayer initiated a "*multi-center, single arm study to assess the safety, bleeding pattern, discontinuation rates (compliance), pharmacokinetics, and efficacy of the ultra-low dose LNG intrauterine contraceptive system (LCS) in adolescents between menarche and 18 years of age over 1 year*". As it can be seen in the current SmPC cited in subsection 3.1.6.1 above, the results of this study are now part of the SmPC and the wording "*[...] Efficacy is expected to be the same for adolescents under the age of 18 as for users 18 years and older [...]*" was accepted within a variation after the initial MA decision was adopted.

3.1.6.3. Regulatory status in view of the current state of medical knowledge

In the EU and the US, the current state of scientific knowledge regarding efficacy and safety of IUD use in postmenarcheal adolescent girls seems to be adequately covered in the informative texts, at least based on the limited publications and guidelines evaluated in preparation of this thesis. According to eligibility criteria published by the WHO (7), LNG IUDs would be category II and "*the advantages of using the method generally outweigh the theoretical or proven risks*", see section 1.1.3 above. As many adolescents would be expected to be nulliparous, warning with regard to limited experience in nulliparous women can reasonably be expected to often be relevant when deciding about suitability for the individual

adolescent girl. Furthermore the possible risk of an induction of a treatment-related infertility in (young) nulliparous women needs to be thoroughly considered. Respective warnings were found in the assessed informative texts from the EU and USA.

3.1.7. Implants

According to PharmNet.Bund (42) there is one implantable contraceptive medicinal product on the German market which is Implanon NXT and it contains the active ingredient ETG, it is therefore a progestogen only contraceptive. It will be implanted subcutaneously and will be effective for a time period of 3 years according to the SmPC (93) .

3.1.7.1. Information concerning the adolescent population found in the PI

The current SmPC for Implanon NXT (93) found in the MRI states the following information focusing on the paediatric population:

Section 4.1: *“Therapeutic indications: Contraception. Safety and efficacy have been established in women between 18 and 40 years of age.”*

Section 4.2: *“[...] Paediatric population: The safety and efficacy of Implanon NXT in adolescents under the age of 18 have not been established.”*

Section 5.1: *“[...] although etonogestrel inhibits ovulation, ovarian activity is not completely suppressed. Mean estradiol concentrations remain above the level seen in the early-follicular phase. In a two-year study, in which the bone mineral density in 44 users has been compared to that in a control group of 29 IUD-users no adverse effects on bone mass have been observed. [...]”*

Although this study on BMD was performed in the adult population, it is noteworthy that effects of suppressed ovarian activity and consequently lowered E2 levels on bone mass have been investigated in clinical study of 2 years´ duration with 44 NuvaRing users and 29 IUD-users in the control group. As discussed above, the effects in postmenarcheal adolescent girls during peak bone mass accrual might differ from those in adult women who have (probably) already reached their peak bone mass.

In the USA, a subdermally inserted implant called Nexplanon (ETG) is authorised. The Prescribing Information states the standardised information repeatedly cited above, it is, however, mentioned that *“[...] no clinical studies have been conducted in women less than 18 years of age”* (94). The Drug Summary can be found in the online version of the PDR (95). As for other products discussed above, the Drug Summary states that Nexplanon is *“not indicated for use premenarche”* and no further information or warnings, respectively, with focus on postmenarcheal adolescents are given.

3.1.7.2. Regulatory considerations

In the EU, Implanon NXT was licensed based on a full dossier in the DCP NL/H/0150/001, the procedure ended with the final outcome “approvable” on 24.12.1998. Unfortunately, no PAR is available at the official MRI on the website of the HMA.

As it is clearly stated in the EU SmPC that safety and efficacy of Implanon NXT in adolescents under the age of 18 have not been established, even indicated in the indication in section 4.1, prescription of Implanon NXT to postmenarcheal adolescent girls below 18 years would be regarded as an “off-label use”. The prescribing physician will have to take more responsibility and will –in doubt- have to justify, why the individual benefit-risk assessment has made him decide that Implanon NXT is an adequate choice for that individual adolescent girl.

3.1.7.3. Regulatory status in view of the current state of medical knowledge

According to eligibility criteria published by the WHO (7), LNG/ETG implants are assessed to be category I. However, based on the information in the SmPC discussed above, it seems as if efficacy and safety has not yet been adequately investigated by the MAH in adolescent girls for the only implant authorised in Germany so far. This information is, however, clearly stated in the SmPC.

For *Nexplanon*, which is authorised in the USA, no information on the conduct of clinical studies in postmenarcheal girls to support the MAA has been revealed by the author.

3.2. Non-hormonal contraceptives

3.2.1. Copper IUD

Comparable to hormonal IUDs, copper IUDs are used by about 6% of all women of reproductive age in Germany according to the DGGG (see section 1.1.2). As this is regarded to be relevant, copper IUDs will also be shortly addressed although from a regulatory point of view they are a medical devices like condoms or diaphragms in the EU (96; 97). One of the representative samples for an Intra Uterine System (IUS) according to a brief internet research and listed in the “Rote Liste online” seems to be GyneFix 200/-330 intrauterines Implantat. Different to other T shaped copper IUDs like e.g. Femena Cu375 (98), GyneFix 200/-330 intrauterines Implantat needs to be sewn to the top of the uterus muscle with a surgical string in a minor surgical procedure to anchor it.

3.2.1.1. Information concerning the adolescent population found in the PI

According to information found in the “Rote Liste online” on the medical device GyneFix 200/-330 intrauterines Implantat (97), this medical device is indicated for contraception for up to 5 years and as emergency contraceptive if inserted within 5 days after unprotected intercourse (99; 100).

There is also a version called GyneFix mini which is advertised by the manufacturer to be especially eligible for young, nulliparous women (101). GyneFix mini is not listed in the “Rote Liste online” and information seems to be only available on the manufacturer’s homepage which states that further information for healthcare professionals will be provided on special request. Further information was requested and the company provided it within a couple of days.

For the copper IUD Femena, there is a package leaflet (PL; “Gebrauchsinformation”) online available (98). This PL does not have a special subsection on paediatric population. It states, however, that “*due to infection risks and their possible consequences (sterility), the insertion of the IUD in nulliparous women should be preceded by thorough evaluation of the desired advantages and the possible therapeutic risks*”, which is a relevant information for the prescribing physician in this context as many postmenarcheal adolescent girls can be expected to be nulliparous. Noteworthy, no such warning has been found in the information provided by the company for GyneFix mini. One leaflet type of information states that the device can be used directly after menarche in women of all age classes (see Annex I for the German leaflet).

The US American Prescribing Information for the intrauterine copper contraceptive ParaGard states that “*safety and efficacy have been established in women over 16 years old*” (102). Similarly, the subsection on “pediatric dosage & indications” in the Drug Summary for ParaGard (103) states that it is indicated for post menarcheal girls above 16 years, which is the only age restriction found in an US American Drug Summary within the research performed in preparation of this thesis. No further information exclusively focusing on postmenarcheal girls was found. The information that “*insertion into a uterine cavity <6 cm may increase incidence of expulsion, bleeding, pain, and perforation*” would, however, be regarded to be also of special relevance in this subpopulation. A contraindication for women with “*current behaviour suggesting a high risk for PID*” could also be of special relevance at an age, when a relationship could be expected to be less stable.

3.2.1.2. Regulatory considerations

No relevant further regulatory information could be located within publicly available sources known to the author, which could be expected as IUDs are medical devices in the EU (104). Even not investigated in depth for the US American market, the same seems to be true in the USA. According to the book “*Developing New Contraceptives: Obstacles and Opportunities*” (105) already dated 1990 “*with the 1976 Medical Device Amendments [...], Congress required scientific evidence of safety and effectiveness prior to marketing new medical devices—including IUDs, many of which were not adequately regulated prior to that time*” (underlined by the author).

The manufacturer states on his homepage (101) that GyneFix has a CE-certificate and that it has been distributed in the European market for many years. In the EU, medical devices are categorised into different “risk-classes”, IUDs are classified in category III (106). Medical devices of the highest risk class III need, beside others, to be assessed based on clinical data. These clinical data need to be adequate to assess possible side effects and finally a positive benefit-risk balance (107). Similar to medicinal products, class III medical devices must be furthermore surveyed while being marketed and e.g. adverse events and market withdrawals must be reported to the national competent authorities, for example the BfArM in Germany. Responsible for medical devices in the USA is the FDA (108).

3.2.1.3. Regulatory status in view of the current state of medical knowledge

According to information found in a publication of “pro familia” from 2009 (109), there are few data available on the safety and efficacy of copper IUDs in nulliparous women, as only parous women were included in the published, larger and controlled clinical trials: Comparing frameless copper IUS like GyneFix with copper IUDs like Femena showed no advantage in the majority of women. The publication summarises that for nulliparous and young women, there is a lack of clinical data on contraceptive efficacy and safety. Possible adverse events like expulsion rates and early removal rates due to an unfavourable bleeding pattern have not been adequately investigated, as clinical studies e.g. did either exclude nulliparous women or did not analyse and report the results stratified by parity. It is therefore not known if, for example, young or nulliparous women should preferably be treated with smaller IUDs (109).

According to the WHO (7), for young women below 20 years a category 2 recommendation is given (“*A condition where the advantages of using the method generally outweigh the theoretical or proven risks*”), in women of 20 years or older, a category 1 recommendation is given (“*A condition for which there is no restriction for the use of the contraceptive method*”). In content, the WHO publication summarises as follows: “*Risks of pregnancy, infection and perforation are low among IUD users of any age. Heavy bleeding or removals for bleeding do not seem to be associated with age. Young women using Cu-IUDs may have an increased risk of expulsion compared with older Cu-IUD users.*”

4. Discussion

As assessed in the introduction of this thesis, there is a high percentage of sexually active adolescent girls in the EU and the USA for whom adequate contraceptive measures are needed. A relevant part of these girls is very young and can be expected to be not yet fully grown. The medical need for safe and effective contraceptives in sexually active, postmenarcheal adolescent girls is therefore beyond dispute.

According to publications discussed in section 1.1.2, physicians prescribe COCs to most of the adolescent girls without cardiovascular risk factors. This is in line with the majority of recommendations given by medical scientific societies. COCs often induce a favourable bleeding pattern which might be of special relevance in adolescent girls, especially those with dysmenorrhea or heavy menstrual bleeding. Also, as discussed in more detail below, limited data would rather question clinically relevant effects on bone metabolism and peak bone mass accrual for COCs containing 30 µg EE. As a consequence of differences in the associated cardiovascular risks, COCs with a lower incidence of VTEs (e.g. EE + LNG) should be preferentially prescribed compared to 3rd generation COCs (e.g. EE + DRSP). The effect of different types of progestogens on the risk of venous (and arterial) thromboembolism was thoroughly assessed in an Article 31 referral which was started in 2013 by the EMA (110).

However, also other hormonal contraceptives like e.g. POPs, transdermal patches, implants or intravaginal rings are currently prescribed to adolescent girls, even though less often than COCs. Please be referred to section 1.1.2 for details on differences in the current use of contraceptives. As also discussed in section 1.1.4, POPs should be preferably prescribed for contraception in adolescents with cardiovascular risk factors that are not eligible for COCs. Due to possible detrimental effects on bone metabolism, depot injections should only be prescribed if other contraceptive methods are considered unsuitable or unacceptable, e.g. for women with “compliance issues”.

European and US American regulatory guidelines discussed in section 1.1.5 have not clearly addressed the need for additional clinical studies to investigate safety and efficacy in adolescent girls below 18 years so far. However, some aspects with special relevance to adolescent girls have been covered, e.g. “*for products not containing an estrogen and suppressing estrogen secretion from the ovaries*” the need to investigate the “*effect on bone mineral density and/or bone metabolism*” (20). The general advice that the population studied should be “*sufficiently representative*” for all “*key studies*” is also of relevance with regard to this aspect.

Necessary measures to further identify and characterise potential safety concerns post approval are discussed in the Pharmacovigilance Plan. As seen in the RMP for Zoely (section

13.1.1.2), “*safety in postmenarcheal adolescents*” can be defined as an “*important missing information*”. Proposed risk minimisation activities to deal with the risk of absent information were, in this case, only routine activities and the inclusion of a statement in the SmPC that “*safety in adolescents below 18 years has not been established*”.

In Europe, “*all applications for marketing authorisation for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver*” (111). The PIP can demand different kinds of studies conducted in the paediatric population. Depending on the PDCO decision, results need to be available before or after the approval. For some of the medicinal products discussed in the results section above, the PDCO Opinion on the submitted PIP was publicly available. Interestingly, the decisions of the PDCO seem very variable in terms of deciding on a complete waiver of paediatric studies or the necessity of performing PK-studies, studies on tolerability and bleeding pattern or studies investigating efficacy and safety in the paediatric population. An example for a complete waiver justified “*on the grounds that the specific medicinal product does not represent a significant therapeutic benefit*” is the product Qlaira (63).

The SmPC of Qlaira (53) states in section 5.2 that measured E2 plasma concentrations were maximal 66.0 pg/ml and on average 51.6 pg/ml at steady state. The estradiol plasma level “*are a composite of the endogenous estradiol and the estradiol*” according to the SmPC. It is furthermore stated that “*stable minimum estradiol concentrations were maintained and ranged from 28.7 pg/ml to 64.7 pg/m*” No further clinical studies in the adolescent population have been provided in the MAA for Qlaira (60), no warnings with regard to possible detrimental effects on bone metabolism can be found in the SmPC (53). This is noteworthy, as the average E2 plasma concentration found for Qlaira are comparable to other hormonal medicinal products, for which warnings on potential detrimental effects on BMD are listed in the SmPC.

Applicable to all hormonal contraceptives, a short discussion on the relevance of suppression of endogenous E2 on potential detrimental effects on bone metabolism will be provided below:

The existence of a threshold for E2 plasma levels which could be regarded to be “safe in terms of a potential negative influence on bone metabolism” was theoretically discussed in a publication of Barbieri et al. from 1992 (29). However, whether such a threshold exists and which individual level of E2 concentrations could be regarded to be safe in terms of potential detrimental effects on bone metabolism is currently not sufficiently investigated in appropriate clinical studies.

Published data for Visanne (29), a medicinal product containing 2 mg of DNG indicated for the treatment of endometriosis, link suppressed E2 level around the range of 50 pg/ml to negative effects on bone metabolism in adolescents. In the PAR for Visanne (112), mean E2 levels after

treatment with Visanne in adult patients were stated to be 55.3 pg/ml; 95%CI: 44.5 to 66.1 pg/ml, comparable to the mean estradiol (E2) levels observed in adult women treated with Qlaira. According to the published Study Synopsis (113), a study investigating the influence of long-term administration of Visanne on bone mineral density (BMD) of the spine in adolescents (n=103, mean age 15.4+/-1.3 years) with suspected or confirmed endometriosis showed that after 52 weeks of treatment mean relative change from baseline in BMD of the lumbar spine (L2-L4) was -1.2% (SD 2.3%, median -1.2%, 95% CI -1.70% - -0.78%). Changes in whole body BMD after 52 weeks of treatment were also investigated and the increase in whole body BMD was less than it could be expected for this period of time in adolescent girls from published data. Even though the above mentioned results for Visanne are observed in a population of adolescents with suspected or confirmed endometriosis, they indicate that decreased endogenous estrogen levels in the range also observed after treatment with e.g. Qlaira or Zoely could have detrimental effects on bone metabolism. For Zoely, the SmPC states average E2 concentrations of 50 pg/ml after treatment. For the paediatric population, the exposure was found to be 36% lower compared to adult subjects (28), see section 3.1.1. For a comparison, published studies for 75 µg DSG (e.g. Cerazette), found mean E2 concentrations after treatment to be 74 pg/ml (114) and 54.4 pg/ml (115), respectively. The results demonstrated somewhat variability in the E2 concentrations, this could be explained by e.g. different treatment durations, sampling procedures or bioanalytical methods. In the cited study by Rice et al., E2 levels after treatment with 75 µg DSG were around 74 pg/ml in period 12, in period 7 they were found to be approximately 90 pg/ml. It should be noted here that the SmPC for Cerazette, discussed in section 3.1.2.1 as “Delamonie”, which was the name in the DC procedure, states a warning regarding decreased E2 levels and potential effects on BMD in section 4.4 (65). Concentrations below 30 pg/ml would be comparable to concentrations also observed after treatment with depot DMPA for which an associated decrease in BMD is clearly established, see e.g. Welsh et al. (116).

As stated in the EPAR for Zoely (36), in general, the association between the use of hormonal contraception and bone mineral density is controversial. With regard to COCs, according to a review on hormonal contraception and bone density by Isley et al. (117), the body of evidence suggests that adolescents currently using COCs have lower BMD than non-users, however, evidence is limited and clinical implications are unclear. There are data that adolescents and young women who started to use modern COCs with a low dose of 20 µg EE just after puberty did not gain as much BMD as non-users and BMD was found to be generally lower in COC users, a publication by Martins et al. states that there were studies in adolescents and young adult women that found lower BMD among COC users, especially with low dose EE (20 µg) (30). The authors concluded that there is limited evidence that suggest that adolescents and young women (<23 years) who use COCs have a lower BMD and that “*more studies [...] are*

needed. It remains unclear whether COCs prevent young women from attaining their peak bone mass, and whether failure to reach peak bone mass is related to increased risk and osteoporosis in later life”.

The “*Single center, open-label parallel group trial to compare the pharmacokinetics [...] between healthy female adolescents (aged 12-17 years) and healthy female adults (aged 18-50 years).*” for Zoely (118) was part of a PIP, even though it was “just a PK study”, the results led to warnings in section 4.4 of the SmPC (see section 3.1.1.1). For a withdrawn application, a PIP with an “*Open-label, 6-month study to assess bleeding pattern, safety, tolerability of drospirenone in adolescent girls requiring oral contraception*” was found on the EMA homepage (69). A PDCO Opinion on a PIP for an OC containing Estetrol and DRSP can also be found. For the later medical product, the MAA is not yet submitted, according to information found on the company’s homepage (119). According to the PDCO Opinion (120), efficacy and safety will have to be investigated in the study named “*Open-label, randomised, comparative study to evaluate the contraceptive efficacy, safety and acceptability of a combined oral contraceptive (COC) containing Estetrol Drospirenone and a marketed COC containing estradiol valerate and dienogest for 13 cycles in adults and adolescents.*”

In case information on the RMP was available, it was seen that some listed “*safety in postmenarcheal adolescents*” as an “*important missing information*”, e.g. for Zoely (36) and Seasonique (38). The RMP of Seasonique listed decreased bone density as an “*important potential risk*”. The RMP of Apleek (86) didn’t list “*use in women under 18 years of age*” as an “*important missing information*”. An adequate RMP should help to ensure valid post marketing surveillance, as according to the “*Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population*” (39), “*normally the pediatric database is limited at the time of approval. [...] and long-term follow-up studies may be important to determine effects [...] on growth and development of pediatric patients. [...]*”.

In Summary, the results of clinical studies performed in adolescent girls and/or the need to conduct such studies has not always been discussed in detail within regulatory assessments. In some of the provided PARs this topic has even not been discussed at all. Taking a look at the PIPs, one can see that the decisions to grant a waiver or to demand or agree to defer clinical studies also varied a lot. The same is true for the coverage of this topic in the RMPs.

It should be noted that especially with regard to the PDCO opinions we have little insight into the grounds on which the decisions have been taken. It must also be noted that the general scope of the PDCO rather is to give incentives for the development of medicinal products with adequately proven efficacy and safety in the paediatric population. It seems that for the indication “*contraception*”, the need to gain reliable data on efficacy and safety in the

adolescent population has rather not been seen to be of major interest. This might also have been due to the fact, that if an agreed PIP is adequately followed to (“PIP compliance”), the Marketing Authorisation Holder (MAH) will get 6 months extension of the Supplementary Protection Certificate (SPC) (121).

The responsibility to demand and assess adequate clinical data in the adolescent population might be somewhat unclear addressed: responsibilities for the adequacy of the demanded data available pre- and post-marketing could be taken by the ChMP (Rapp/Co-Rapp, OMS) or RMS (and CMSs), by the PDCO and by the PRAC (only post-marketing).

In the results sections above, a closer look at the SmPC of some currently marketed contraceptives has been taken to investigate, if and how information on the results or absence of results of clinical studies in the paediatric population, here postmenarcheal adolescent girls, have been provided. The information provided differed notably among the different products, see section 3 for details. Although the requirements for the content are clearly described in the EC SmPC Guideline (24), not all of the current SmPCs had a subsection on the “paediatric population” in section 4.2 “*Posology and method of administration*”. It was therefore often not clear, if clinical studies to investigate efficacy and safety have been performed by the applicant. For older medicinal products the MAH could either just state that such studies have not been conducted or rely on published data of investigator-initiated-trials to justify that efficacy and safety have been established. These changes would, however, have to be submitted via Type II variation and agreed to by the NCA, RMS and CMS or ChMP, depending on the type of the initial authorisation procedure.

The FDA guidance “*Labelling for Combined Oral Contraceptives*” (26) from 2004 discussed the use of a standard term in the “paediatric use” section, stating that “*safety and efficacy are expected to be the same for post pubertal adolescents and adult women. OCs are not indicated before menarche.*” This information is now found in most of the prescribing information for US American contraceptives, see result section above. In the opinion of the author and in line with all issues discussed in this thesis, the information that “*safety and efficacy are expected to be the same for post pubertal adolescents and adult women*” seems to be inadequate, at least for some of the contraceptives discussed above.

In line with the recommendations of the medical scientific societies, the regulatory guidelines and aspects discussed within the PARs, the most important clinically relevant risk which might differ disadvantageously in young adolescent girls, might be the potential effect on bone metabolism discussed in detail above.

Potential differences in the bleeding pattern could negatively influence the compliance. In a worst case scenario, potential differences in the bleeding pattern could, however, also lead to increased rates of iron deficiency and anaemia in adolescent girls.

In line with the recommendations of the Guideline on Clinical Investigation of Steroid Contraceptives in Women (18), as already discussed in section 1.1.5.1, plasma concentrations of ovarian steroid (including estrogens) need to be investigated and suppression of E2 needs to be discussed in the light of its physiological effects on bone metabolism.

If the medicinal product applied for leads to decreased E2 serum levels, there is a potential risk that treatment leads to a decrease in bone mineral density in the adolescent population which could reduce peak bone mass and increase the risk for fracture in later life. In such a case, BMD after treatment in adults and adolescents needs to be further investigated. If this has not been done before the MAA has been submitted, it could potentially be an “Imposed mandatory additional pharmacovigilance activity (key to benefit risk)” in the sense of section III.4.1 of the Good Pharmacovigilance Practice (GVP) Guideline (21). Until the results such studies would be available, a clear warning with regard to potentially clinically relevant effects on bone mineral density should be included in the SmPC and PL. The treating physician should be informed that treatment leads to decreased E2 serum levels and that this could lead to a decrease in bone mineral density which could reduce peak bone mass and increase the risk for fracture in later life. The physician must then weigh the potential benefits of the treatment against the potential risks for each woman.

Clinical studies in adolescent girls, which might not necessarily be available at the time of the assessment of a positive benefit risk ratio during assessment of the initial MAA, would be studies which assess efficacy somewhat closer to the “real world”. In line with what was discussed in the US American Advisory Committee Briefing Document (17) already cited in section 1.1.4, “actual use data” closer to “real world data” in the postmenarcheal adolescent population would be highly appreciated. As stated in the publication “Contraception in adolescents” (2014) in the official journal of the American Academy of Paediatrics (AAP) (15), typical use failure rates might be higher in adolescents, an assumption which is regarded to be reasonable. The AAP publication also states that (underlined by the author) “[...] *comparing the efficacy of different methods, it is important to distinguish between typical use and perfect use, and counselling should be on typical use*”. To enable such a counselling, information on typical use from observational post-marketing studies need to be provided to the prescribing physicians.

To address some of the potential weaknesses of this work, it must be noted that it focused on hormonal contraceptives and other contraceptive options like e.g. copper IUDs or barrier methods have only been briefly considered. Only a couple of examples, for which data like

PARs, PDCO Opinions and SmPCs were publicly available have been discussed. The search strategy has been based on personal preferences and no systematic review process has been pre-defined. Important publications or (E)PARs might not have been found. While screening for relevant information, important sections in the (E)PARs or other comprehensive publications might have been overlooked. The US American regulatory requirements and Prescribing Information have only very briefly been discussed. The same is true for a possible non-clinical approach to investigate some of the relevant aspects. In the author's opinion these potential drawbacks are, however, acceptable as this work and the provided arguments for discussion should rather focus on calling attention to an area, which should be paid more attention to.

As the final assessment of a MAA will always be based on considerably more data and probably repeated discussions with the applicant, other OMS/CMS, the ChMP and also within the responsible team of assessors, it should be clearly stated that none of the regulatory decisions taken and discussed in this thesis would be judged as clearly "right" or "wrong" by the author. However, there are some lessons to be learned, which will be dealt with in the following "Conclusions".

5. Conclusion

A considerable subset of (very) young postmenarcheal girls is using contraceptives, and efforts have to be taken that safety and efficacy of contraceptives are adequately investigated in this population. If data gained in clinical studies in adult women are not sufficient to achieve this, additional studies in young postmenarcheal women are needed. Until the results of such clinical studies are available, the absence of information from clinical studies needs to be clearly labelled in the SmPC and PL. If, in absence of these clinical study results, it cannot be concluded on a positive benefit-risk balance in postmenarcheal adolescent women, the indication should be restricted to adult women and respective warnings should be included.

Assessment Reports (ARs) of MAAs should discuss, if clinical studies in postmenarcheal girls would have been required to assess specific clinical aspects, which could not be covered by clinical studies conducted in adult women. If studies in postmenarcheal girls have been conducted, their results need to be discussed in detail. Noteworthy, in some of the provided PARs, the use in adolescent girls was not discussed at all. This might be partly explained by the fact that OCs have been marketed for a long time. The FDA labelling recommendation for OCs (26) stating *“efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older”* might be representative of the general assessment of the medical scientific societies, so far. However, potential differences in tolerability (e.g. bleeding pattern, adverse events) could affect compliance and finally also contraceptive efficacy in the “real world”. Further on, the situation might differ for other contraceptives like e.g. IUDs, which was, however, considered in the investigated PARs. The FDA labelling recommendation also kind of distracts from potential safety aspects, which are less well investigated, e.g. potential detrimental effects on bone metabolism. Taking a look at the PDCO Opinions on PIPs, the decisions to grant a waiver or to demand or agree to deferred clinical studies varied a lot. The same is true for the coverage of this topic in the RMPs.

Therefore, for contraceptives, further efforts should be taken to harmonise the assessment of clinical data relevant to postmenarcheal girls and the subsequent information in the SmPC and PL.

For products already authorised, the MAHs should amend SmPCs and PLs via variation to provide currently available data. If there are no data available and the safety and efficacy of the concerned medicinal product in adolescents below 18 years has not yet been established, this should also be clearly stated.

Competent authorities should also ask for such amendments, based on thorough discussion in the submitted Justification Documents, within Renewal- or PSUR-ARs.

6. Summary

There is a relevant percentage of young sexually active adolescents for whom safe and effective contraceptives are needed. According to a guideline published by the German Society of Gynaecology and Obstetrics (4), there were approximately 1.5 million women between 14-19 years of age taking oral contraceptives (OCs) in Germany in 2010. Contraceptive measures other than OCs, like e.g. transdermal patches, intravaginal rings or implants, were used only by a minority of all women.

There is no specific guidance on evaluation of efficacy and safety in the adolescent population in the current official European guidance on the regulatory requirements for the registration of hormonal contraceptives, already issued in the year 2000 (20). Some aspects covered in the guideline, like e.g. the need to investigate the influence of the new contraceptives on ovarian function and endogenous estrogen production, are, however, of special relevance for the adolescent population. Decreased endogenous estrogen levels as a consequence of ovarian suppression could lead to a decrease in bone mineral density. In adolescent girls and young women, potential detrimental effects on bone metabolism could reduce peak bone mass and increase the risk for fractures in later life.

The current work focused on hormonal contraceptives, other contraceptive options like e.g. copper Intra Uterine Devices or barrier methods have, however, also been briefly considered. Based on some representative examples, it was evaluated, if clinical data on efficacy and safety in postmenarcheal adolescent girls have been provided and assessed during Marketing Authorisation Applications and/or later in the “regulatory life-cycle”. For this reason, the information provided in the SmPCs of different contraceptives has been checked for relevant information on clinical studies performed in the paediatric population. When Public Assessment Reports were available, it was investigated if efficacy and safety in the paediatric population had been separately discussed and if any potential need for further investigation in clinical trials in adolescents had been addressed. Special obligations in the Paediatric Investigation - or Risk Management Plan to further investigate the use in postmenarcheal adolescent girls, e.g. in post-marketing studies after authorisation, have also been considered.

In some of the provided Public Assessment Reports, the use of contraceptives in adolescent girls was not discussed at all. In the assessed PDCO Opinions on Paediatric Investigation Plans, the decisions to grant a waiver or to demand or agree to defer clinical studies varied considerably, the same is true for the coverage of this topic in the Risk Management Plans.

In summary, for contraceptives, further efforts should be taken to harmonise the assessment of clinical data relevant to postmenarcheal girls and the respective information given in the SmPC and PL.

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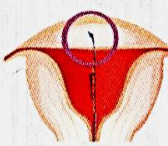
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Annex

Leaflet provided by the manufacturer of *GyneFix mini*:


Die Kupferkette GyneFix® auf einen Blick

Neuartige Verankerung




daher kein Verrutschen mehr möglich und keine unnötigen Reizungen der Gebärmutterwand, wie bei herkömmlichen T-förmigen Spiralen.

Ohne Hormone

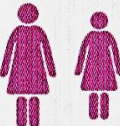


somit keine systemischen Nebenwirkungen oder Belastungen für das Herz-Kreislaufsystem




und auch keine Gewichtszunahme, Hautveränderungen oder Wechselwirkungen mit anderen Medikamenten (z.B. Antibiotika).

Auch für junge Frauen geeignet




Aufgrund der sehr schmalen und kleinen Form der Kupferkette GyneFix® ist sie auch für besonders kleine Gebärmütter geeignet. Die Kupferkette kann ab der ersten Menstruationsblutung eingesetzt werden und ist für Frauen jeder Altersgruppe geeignet.

GyneFix® Ärzte




Da die Kupferkette GyneFix® besonders ist, legen Ärzte, die sie anbieten möchten, ein spezielles Training hierfür ab. Daher sollte man immer gleich zu einem trainierten GyneFix®-Arzt gehen, um die volle Sicherheit der Methode zu erhalten.

Verhütungsschutz für 5 Jahre



- 5 Jahre Langzeitverhütungsschutz bei kontinuierlicher Sicherheit – sowohl mit GyneFix® 200 als auch mit GyneFix® 330.
- Eine frühzeitige Entfernung ist jederzeit möglich.

99,9 % Verhütungssicherheit



da Anwendungsfehler, wie

- Vergessen,
- Erbrechen/Durchfall
- Wechselwirkungen,
- & Verhütungsfehler nicht möglich sind.

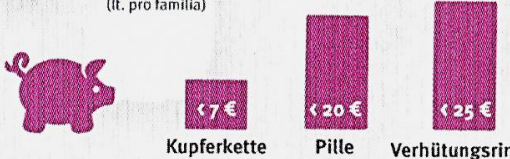
Keine verstärkte Menstruationsblutung

Berichte über verstärkte Blutungen oder Schmerzen innerhalb des ersten Anwendungsjahres: (Rasheed et al.)


Verhütungsmittel	Prozent
Kupferspirale	42 %
Kupferkette	3 %

Geringe Verhütungskosten

Durchschnittliche monatliche Verhütungskosten für unterschiedliche Verhütungsmittel: (lt. pro familia)



Verhütungsmittel	Kosten (€)
Kupferkette	< 7 €
Pille	< 20 €
Verhütungsrin	< 25 €

 Sie haben noch Fragen oder benötigen etwas?

0711/7 2254808 oder gyn@verhueten-gynefix.de

Hormonfreie Verhütung – aus Liebe zur Frau entwickelt

Weitere Infos auch unter: www.verhueten-gynefix.de

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.