Revision 1
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Rationale for the triggering of procedure under Article 107i of Directive 2001/83/EC on cyproterone/ethinylestradiol (2mg/0.035mg) presented by ANSM, France

Disclaimer :

This assessment report was provided by the French Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the French Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the French Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

Agence nationale de sécurité du médicament et des produits de santé

RÉPUBLIQUE FRANÇAISE

Benefit/risk review of cyproterone acetate (2 mg) and ethinylestradiol (0.035 mg) combination containing medicinal products

French National Agency for Medicines and Health Products Safety – ANSM

15th February 2013

SUMMARY

Introduction

DIANE 35 has been granted a Marketing Authorisation (MA) in July 1987 in the following therapeutic indication "Treatment of acne in women: the efficacy is moderate and only observed after several months of treatment."[1]

DIANE 35 is a combination of an anti-androgen and a low-dose oestrogen: 2 mg of cyproterone acetate and 35 µg of ethinylestradiol. It has the properties of both substances.
- Cyproterone acetate has a specific anti-androgenic effect due to its competitive inhibition of 5-α dihydrotestosterone binding at the cytosolic receptor of target cells - an action that stops sebum production and excretion as well as hair development.
As a 17-α-hydroxyprogesterone derivative, cyproterone acetate also has progestogenic action. The antigonadotropic action of the cyproterone acetate is additive to the one of ethinylestradiol. Cyproterone acetate has an antioestrogenic action. It does not interfere with adrenal cortex function.
- The 35 µg of ethinylestradiol have a trophic effect on the endometrium and an antigonadotropic effect.

In France first generics were marketed in 2003. Nowadays 11 out of 17 generics of Diane 35 are marketed and, represent 70-80% of the French market.

Special warnings relating to the venous and arterial thromboembolic risks have been introduced in the SmPC since October 1987 and updated according to the European estro-progestative core SmPC in 1998 and 2011.

In the context of the review of the benefit/risk ratio of all French marketing authorisations granted before 2005, the review of the benefit/risk ratio of Diane 35 was initiated in 2011.
In this context, the MAH Bayer provided the ANSM a summary of efficacy and safety data on the use of this medicinal product in the treatment of acne and with data on Diane 35's contraceptive efficacy with a proposal to extend the therapeutic indication to include women to be treated for acne and seeking contraception.

Finally, the ANSM considers, on 30 January 2013 that the benefit/risk ratio of Diane 35 is unfavourable in the treatment of acne and announces its plan to suspend the marketing authorisation of Diane 35 and its generics in France within 3 months.

[1] A marketing authorisation was granted to Diane (called also Diane 50 due to its composition of 50 µg of ethinylestradiol and 2 mg of cyproterone acetate), its therapeutic indication was Hyperandrogenism. This marketing authorisation was withdrawn the 24 April 2001 due to a non renewal of the marketing authorisation. Diane was marketed from 1982 to 1987 in France.

Use of Diane 35 and its generics in France

- **Sales**

In France it is estimated that Diane 35 (and generics) represents 6% of sales of all Combined Oral Contraceptives (COCs) + Diane 35 sales.

Nowadays, generics represent 70-80% of the sales. The most sold generic is Minerva (a Bayer generic) and Diane 35 is on the 2nd rank. Thus Bayer holds around 45% of the French market.

- **Prescribers**

Sales figures according to the type of prescriber indicate that the liberal distribution prescription (from IMS-Xponent) is as follows:

- GPs: 60%
- Gynaecologists: 37%
- Dermatologists: 3%

The indication for prescription according to the physician status (from IMS-GPs panel) issue is as follows:

	Acne	**Contraception**
Dermatologists	94%	-
GPs	7%	89%
Gynecologists	5%	77%

Diane 35 in Europe

Diane 35 has a Marketing Authorisation (MA) in 135 countries and is marketed in 116 countries.
In most of these countries, the therapeutic indication is “acne” or “androgen dependent disease”, although some countries (Ireland for example) have coupled in the indication labelling, contraception to acne.

Moreover in some countries (AT, BE, UK and IE) the therapeutic indication of Diane 35 is labelled as severe acne.

European SmPC of Diane 35

Member state	4.1 Therapeutic Indications	4.2 Posology and method of administration
AT Cypro-ethinyl acis 2 mg/0.035 mg film-coated tablets	Signs of androgenisation in women requiring hormonal treatment: - Acne, severe forms when accompanied by inflammation or nodular formation (papulopustular acne, nodulocystic acne) or if there is a risk of cicatrisation and hence topical treatment alone is unlikely to be successful. The hormonal treatment should be weighed up against systemic antibiotic therapy. - Milder forms of hirsutism. - Androgenetic alopecia. *Note:* Although Cyproethinyl acis also has a contraceptive effect, it should not be used solely for contraception; it should be used only in women who require treatment for the above-mentioned androgen-dependent symptoms (see also: section 4.3 "Contraindications", section 4.8 "Undesirable effects". For duration of treatment, see: section 4.2 "Posology and method of administration"). Complete resolution of acne can be expected in almost all cases, often as early as within a few months. However, in particularly difficult cases, a prolonged course of treatment may be required before complete success is achieved. It is recommended that treatment be discontinued 3 to 4 cycles after complete resolution of symptoms; Cyproethinyl acis should not be continued solely for contraception purposes. If androgen-dependent symptoms recur, treatment with cyproethinyl acis can be re-administered.	Cyproethinyl acis suppresses ovulation and thus has a contraceptive effect. Patients using Cyproethinyl acis should therefore not use an additional hormonal contraceptive, as this will lead to a hormone overdose and is not required for effective contraceptive protection. For this same reason, women wishing to conceive should not use Cyproethinyl acis. Cyproethinyl acis must be taken regularly to achieve a sufficient therapeutic effect and an effective contraceptive action.(…) *Duration of treatment* The duration of treatment depends on the severity of the signs of androgenisation and their response to therapy. In general, therapy over several months is required. Acne and seborrhoea generally require a shorter course of treatment than hirsutism and alopecia. It is recommended that treatment be terminated 3 to 4 cycles after complete resolution of symptoms. The therapeutic approach should be reviewed if the therapeutic response is absent or insufficient in cases of: - severe acne or seborrhoea after at least 6 months of therapy or - alopecia and hirsutism after at least 12 months of therapy. Upon resolution of the signs of androgenisation, a switch to a low-dose oral contraceptive should be made for any woman still wanting contraceptive protection. If androgenetic symptoms recur, treatment with Cyproethinyl acis can be resumed
BE Diane-35,2mg/ 0.035mg comprimés enrobés	For the treatment of severe acne, refractory to prolonged oral antibiotic therapy; moderately severe hirsutism. It should not be used solely for contraception.	Diane-35 should be taken regularly to observe its therapeutic efficacy and its contraceptive protection. Previously used hormonal contraceptive should be discontinued. The posology of Diane-35 is similar to the usual posology of combined oral contraceptives. The same recommendations of administration should apply. Combined oral contraceptives are associated with a failure rate of about 1% per year when properly used. The irregular administration of Diane-35 may lead to breakthrough bleeding and can affect its therapeutic and contraceptive efficacy.
BG	Treatment of androgen disease in women such as acne, especially severe forms accompanied by accompanied by seborrhea or by inflammation or formation of nodules androgenic alopecia and mild hirsutism. Diane 35 also provides an oral contraceptive effect in patient with above mentioned conditions."	Unknown
CZ	Treatment of androgen dependent illnesses (such as acne, hirsutism and alopecia).The SmPC also states that the products should not be used as a contraceptive in case that a woman does not suffer from hyperandrogenism and above mentioned illnesses.	Unknown

EE	Contraception for women with androgen origin acne, seborrhea or mild hirsutism.	Unknown
FR DIANE 35 microgrammes, comprimé enrobé	Treatment of acne in women: the efficacy is moderate and only observed after several months of treatment.	• DIANE 35 microgram coated tablets, initial therapy should be started as follows: 1st cycle: one tablet daily for 21 days starting on the first day of the cycle. Subsequent cycles: after 7 tablet-free days, take the next pack for 21 days. Treatment should be continued for several months, the first signs of clinical improvement appear after 3 or 4 months, sometimes longer. • DIANE 35 micrograms, coated tablet: When changing from an oral estroprogestative contraceptive, should be started as follows: Take the1st tablet preferably on the day after taking the last active tablet of the oral estroprogestative contraceptive, or no later than the day following the usual tablet-off, or the day after taking the last placebo tablet of oral estroprogestative contraceptive. If you miss one or more pills: When the anti-ovulation effect sought, one missed tablet exposes to a risk of pregnancy. If a tablet has been missed within 12 hours of the usual time, a single tablet should be taken as soon as possible and the treatment should be continued as usual. If a tablet has been missed for more than 12 hours of the usual time, the anti-ovulation effect is no longer maintained. Immediately take the last missed tablet and continue the treatment until the end of the pack simultaneously using a mechanical method of contraception (condoms, spermicides, ...) until the resumption of the next pack, including during bleedings. In case of gastro-intestinal disorders: In case of severe gastro-intestinal disorders, absorption of a tablet may not be complete, when the anti-ovulation effect is sought, additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after taking a tablet, the same instructions as given for missed tablets should apply (see above).
FI	Contraception for women with androgen origin acne, seborrhea or mild hirsutism.	Unknown
HU	Women with severe acne that do not respond to long-term treatment with oral antibiotics and also indicated in moderately severe hirsutism. It is not authorised as a contraceptive.	Unknown

IE Dianette 2mg/35 microgram coated tablets	For use in the management of severe acne vulgaris, especially those forms which are accompanied by seborrhoea or by inflammation or formation of nodes (acne papulopustulosa, acne nodulocystica) in women. Oral contraception for the woman suffering from the above. Although Dianette also acts as an oral contraceptive, it should not be used in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent acne described.	How to take Dianette Dianette is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Combined oral contraceptives when taken correctly have a failure rate of approximately 1% per year. (…) Length of use The length of use depends on the severity of the clinical picture. Complete remission of acne is expected within a few months of commencing treatment, but in particularly severe cases treatment for longer may be necessary before the full benefit is seen. It is recommended that treatment be withdrawn 3 to 4 cycles after the acne has satisfactorily resolved and that Dianette is not continued solely to provide oral contraception. Repeat courses of Dianette may be given if the androgen-dependent acne recurs. In this case, an early restart of Dianette should be considered.
IT	Treatment of androgen-dependent skin disorders in women, such as acne of all kinds, with a significant presence of sebum on the skin (seborrhea) and accompanied by inflammatory and nodular manifestations; androgen-dependent hair loss; modest forms of abnormal hair growth on the face and body. Although Diane also acts as an oral contraceptive, it should not be prescribed for contraception should be reserved for those women requiring treatment for the androgen-dependent conditions described above.	Unknown
LV	For treatment of androgen dependent diseases (acne, hirsutism and alopecia) and contraception for women with androgen dependent disease.	Unknown
NL	For treatment of acne, seborroe or mild hirsutism." Although Diane-35 also works as contraceptive, it should not solely be used as contraceptive treatment but should be reserved for women in need of treatment of andrgen dependent disorders specified above".	Unknown
NO	For the treatment of androgen induced acne, severe seborrhea or mild hirsutism. Should only be used by women in need of treatment for acne etc. It is not recemmended as a contraception on its own.	Unknown
PT	Treatment of androgen-dependent diseases in women, such as acne, specially pronounced forms with seborrhoea, inflammation or lumps, androgenic alopecia, mild forms of hirsutism. Also authorised for contraception in women suffering from these conditions. It should not be used as contraceptive out of the indications described above.	Unknown

SE	In Sweden, Diane® is approved only for “treatment of protracted and refractory moderate to severe acne and seborrhoea in women as far as hormonal treatment is considered necessary”. This preparation can only be used up to 3-4 months after the acne complaints have disappeared. It is not approved as a combined oral contraceptive, and in the SmPC it is clearly stated that Diane® should not be used as a contraception method.	Unknown
SI	Medical conditions, dependent on androgen hormones, such as severe acne, and disorders that are accompanied by seborrhoea or even inflammatory changes of the skin with papules and pustules, androgenic alopecia and mild hirsutism. Although tablets also act as oral contraception, they should not be used solely for that purpose. They are intended for use in women who need treatment for listed androgen-dependent skin diseases.	Unknown
SK	Treatment of androgendependent diseases in women, like acne and forms with seborrhea, inflammation or nodular forms, androgenic alopecia and light forms of hirsutism. It should not be used in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent conditions described.	Unknown
UK Co-cyprindiol 200/35 tablets	Co-cyprindiol is recommended for use in women only for the treatment of (a) severe acne, refractory to prolonged oral antibiotic therapy ; (b) moderately severe hirsutism. Although co-cyprindiol also acts as an oral contraceptive, it should not be used in women solely for contraception, but should be reserved for those women requiring treatment for androgen-dependent skin conditions described. Complete remission of acne is to be expected in nearly all cases, often within a few months but in particularly severe cases treatment for longer may be necessary before the full benefit is seen. It is recommended that treatment be withdrawn 3 to 4 cycles after the indicated condition(s) has/have completely resolved and that co-cyprindiol is not continued solely to provide oral contraception. Repeat courses of co-cyprindiol may be given if the androgen-dependent condition(s) recur.	Co-cyprindiol inhibits ovulation and thereby prevents conception. Patients who are using co-cyprindiol should not therefore use an additional hormone contraceptive as this will expose the patient to an excessive dose of hormones and is not necessary for effective contraception.

Diane 35 approved indication in France: anti-acne effect

- **Literature analysis**

In January 2012, a Cochrane review[2] considered randomized controlled trials that compared the effectiveness of combined oral contraceptives (COCs) containing an estrogen and a progestin to placebo or another active therapy for acne in women. Seven studies were identified testing the combination of cyproterone acetate (2 mg) and ethinylestradiol (35 µg) [CPA/EE or Diane 35], 4 studies were randomised and double-blind.

1. Palombo-Kinne - 2009

Randomised, multicenter, double-blind study: Diane 35 vs 4th generation COC vs placebo

This study recently comforts the effect of Diane 35 on acne compared to placebo and to ethinylestradiol/dienogest, (EE/DNG), 4th generation COC[3]:

- N=1138 women, 16 to 45 years old, with mild to moderate facial papulopustular acne treated during 6 cycles
- Primary endpoint: percentage change in inflammatory lesion count (sum of papules, pustules and nodules); percentage change in total lesion count (sum of open and closed comedones, papules, pustules and nodules); and percentage of patients with improvement of facial acne (6-point scale)
- Results: All primary analyses proved that EE/DNG was superior to placebo and non-inferior to EE/CPA ($p<.05$). For inflammatory lesions, the reduction (+/-SD) rates were:

  EE/CPA: -64.6+/-31.2%
  EE/DNG: -65.6+/-29.9%
  Placebo: -49.4+/-41.0%.

  For total lesions, the reduction rates were -54.7+/-26.3% for EE/DNG, -53.6+/-27.5% for EE/CPA and -39.4+/-33.6% for placebo. The percentages of patients with improvement of facial acne were 91.9% for EE/DNG, 90.2% for EE/CPA and 76.2% for placebo.

EE/CPA was superior to placebo, in spite of the prominent placebo effects, and as effective as EE/DNG in the treatment of mild to moderate acne.

2. Carlborg - 1986

Randomised, multicenter, double-blind study: Diane 35 vs Diane 50 vs 2nd generation COC

- N=133 women, over 15 years of age with at least 8 lesions on the face, treated during 6 cycles
- Primary endpoint: percentage change in lesion count
- Results: no significant difference between Diane 35 and 50 on the total number of acne lesions with greater reduction compared to levonorgestrel/ethinyl (LNG/EE). The reduction (+/-SD) rates were:

  EE/CPA 35: -61+/-31%
  EE/CPA 50: -51+/-52%
  LNG/EE: -27+/-52%.

After only 4 months of treatment, the patients on Diane 35 and Diane 50 had a significantly greater reduction in the number of acne lesions compared with those on LNG/EE. Diane 35 had a tendency towards less pronounced "estrogenic" side effects and was equally effective in the treatment of acne as Diane 50.

3. J&J - 2005

Randomised, double-blind study: Diane 35 vs Tricilest /Triafemi (3rd generation COC)

- N=48 women, 15 to 49 years with moderate acne vulgaris treated during 3 cycles
- Primary endpoint: change in total lesion count from baseline to latest available evaluation
- Results: no significant difference between both arms on the total number of acne lesions (norgestimate 180-215-250µg + EE 35µg vs Diane 35).

[2] Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Combined oral contraceptive pills for treatment of acne, Cochrane Database of Sytematic Reviews 2012, Issue 7

3 Palombo-Kinne E, Schellschmidt I, Schumacher U, GräserT. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate.Contraception 2009; Vol. 79, issue 4:282–9.

In this small trial, the study groups were not significantly different for mean change in total lesion count and discontinuation due to adverse events at cycle three.

4. Aydinlik - 1986

Randomised, multicenter, double-blind study: Diane 35 vs Diane 50

- N=425 women of reproductive age with mild to moderate acne and seborrhea treated during 9 cycles
- Primary endpoint: healing or improvement of acne cases from baseline.
- Results: no significant difference between Diane 35 and 50 in acne outcomes and discontinuation rates.

5. Vartiainen - 2001

Open, randomised, multicenter study: Diane 35 vs 3rd generation COC

- N=172 women, aged 16 to 35 years with acne treated during 6 cycles
- Primary endpoint: acne lesion count
- Results: reduction in acne with the combiphasic COC desogestrel / ethinylestradiol (EE/DSG) comparable to Diane 35: the relative numbers of comedones, papules and pustules at cycle 6 significantly decreased to 37%, 38%,and 19% in the EE/DSG group and to 24%, 36% and 17% in the EE35/CPA group, respectively. All reductions were statistically significant ($p < or = 0.003$) at both cycles 3 and 6.

There was no statistically significant difference between the two treatments. In both groups, the majority of women with severe acne shifted to a less severe acne category.

6. Dieben - 1994

Open, randomised, multicenter study: Diane 35 vs 3rd generation COC

- N=183 women, aged 18 to 35 years with at least 5 facial acne lesions treated during 4 cycles
- Primary endpoint: acne lesion count
- Results: reduction with regard to the number of lesions and the degree of severity observed in both groups: the combiphasic COC desogestrel / ethinylestradiol (EE/DSG) and Diane 35.

No differences were found between the two treatments in the clinical and photographic evaluation.

7. Fugere - 1988

Randomised, two-center, double-blind study: Diane 35 vs Diane 50

- N=62 women aged 17 to 35 years, with moderate to severe acne, treated during 12 cycles
- Primary endpoint: acne lesion count
- Results: no statistically significant difference in the total number of acne lesions between the two treatments.

Both formulations of Diane were effective in improving acne, even in women who had been refractory to other antiacne medication. There was no advantage of the highest dose of ethinylestradiol combined with 2 mg of cyproterone acetate for the acne long-term therapy.

The Cochrane review concludes that the combination of cyproterone acetate (2 mg) and ethinylestradiol (35 µg) shows an efficacy in acne comparable to other COCs combined to levonorgestrel (1^{st} generation COC), desogestrel (2^{nd} generation COC), norgestimate (3^{rd} generation COC), or dienogest (4^{th} generation COC). Besides 50 µg of ethinylestradiol combined to 2 mg of cyproterone acetate (Diane 50) did not show a higher efficacy on acne compared to Diane 35.

It should be noted that in the documents submitted by Bayer in response to our request for a benefit/risk review, provided studies were different from the studies selected by the Cochrane review, they are detailed thereafter.

- **Diane 35 position in the therapeutic management of acne**

The approved indication of Diane 35 in France is as follows:
"Treatment of acne in women. The efficacy is moderate and only observed after several months of treatment."
Of note: the indication of contraception was not granted in 1987 during marketing authorisation procedure given that submitted data did not allow establishing adequately a Pearl index for Diane 35 combination.

In the French 2007 guideline of the acne treatment[4], hormone therapy for acne is recommended only in the maintenance treatment of acne. This maintenance treatment is mainly based on topical retinoids (adapalene). In women seeking oral contraception, a non-androgenic hormone therapy is recommended. Moreover, this guideline adds that Diane 35 must not be prescribed as a contraceptive during oral isotretinoin treatment.

It is of note that in France only one contraceptive combination has been granted an indication in "*Contraception of acneic women":* it is the triphasic combination of ethinylestradiol (35 µg) and norgestimate (180-215-250 mg)[5].

[4] Recommandations de bonne pratique de l'Afssaps, 2007 : Traitement de l'acné par voie locale et générale

[5] 35 µg of ethinylestradiol and 180-215-250 mg of norgestimate : Triafémi®, Tricilest®.

Efficacy Data of Diane 35 in acne (Cochrane review)

References common to Cochrane review and Bayer's submission	Type of Study	Study Medication	Study Population	Observation	Clinical Parameters	Results
Palombo-Kinne (2009) Palombo-Kinne E, Schellschmidt I, Schumacher U, GräserT. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. Contraception 2009; Vol. 79, issue 4:282–9.	Multicenter trial conducted Mar 2004 to May 2005 (65 centers in Czech Republic, Poland, Russian Federation, Slovakia, and Ukraine) **Double-blind**, three-arm trial; **Random assignment 2:2:1**	0.030 mg ethinylestradiol +2 mg dienogest with placebo and 0.035 mg ethinylestradiol +2 mg cyproterone acetate	**N=1338** women, 16 to 45 years old, with mild to moderate facial papulopustular acne	Treatment duration: 6 cycles	Primary: percentage change in inflammatory lesion count (sum of papules, pustules and nodules); percentage change in total lesion count (sum of open and closed comedones, papules, pustules and nodules); and percentage of patients with improvement of facial acne (6-point scale) Secondary: Investigator Static Global Assessment at each visit [six-point scale from normal to highly inflammatory]; absolute changes in facial lesion count over time; patient's self-assessment at end of therapy.	All primary analyses proved that EE/DNG was superior to placebo and non-inferior to EE/CPA ($p<.05$). For inflammatory lesions, the reduction (+/-SD) rates were -65.6+/-29.9% for EE/DNG, -64.6+/-31.2% for EE/CPA and -49.4+/-41.0% for placebo. For total lesions, the reduction rates were -54.7+/-26.3% for EE/DNG, -53.6+/-27.5% for EE/CPA and -39.4+/-33.6% for placebo. The percentages of patients with improvement of facial acne were 91.9% for EE/DNG, 90.2% for EE/CPA and 76.2% for placebo. EE/DNG was superior to placebo, in spite of the prominent placebo effects, and as effective as EE/CPA in the treatment of mild to moderate acne, thus proving a valid option for the treatment of acne in women seeking oral contraception. No information on who was blinded, no information on how randomization schedule was generated.
Carlborg L (1986) Cyproterone acetate versus levonorgestrel combined with ethinyl estradiol in the treatment	Multicenter **comparative trial** in Sweden.	DIANE 35 vs DIANE (50)1 vs Microgynon[2]	**N=133** women over 15 years of age with at	4-week washout period for acne	Acne lesion counts. Gynecologist, dermatologist and participant assessment	Significantly better reduction of acne lesions after 6 months with DIANE 35 and

of acne Acta Obstet Gynecol Scand Suppl 134 (1986) 29-32	Clinicians and participants were **blinded**.		least 8 lesions on the face	treatments. 6 treatment cycles 6 months	of acne ("good," "moderate" or "poor")	DIANE (50) than with Microgynon (75 vs 26%).
J&J 2005 Johnson, Johnson Taiwan Ltd. Comparison of efficacy and safety of norgestimate-ethinyl estradiol and cyproterone acetate-ethinyl estradiol in the treatment of acne vulgaris. http://clinicaltrials.gov/ct2/show/NCT00752635 (accessed 25 Aug 2011).	**Randomized controlled trial** conducted in Taiwan from Sep 2004 to Sep 2005 No information on randomization method. **Double-blind** (did not specify who was blinded)	norgestimate 180-215-250 µg plus ethinyl estradiol 35 µg vs cyproterone acetate 2 mg plus EE 35 µg	**N=48** women: 15 to 49 years. with moderate acne vulgaris (grade II or III), 6 to 100 comedones (non-inflammatory lesions), 10 to 50 inflammatory lesions (papules or pustules), fewer than 5 nodules	3-month treatment phase	Primary: change in total lesion count from baseline to latest available evaluation. Secondary: change in inflammatory lesion count, change in individual lesion count, percentage of participants showing improvement on investigator's global assessment, participant's end-of-therapy self-assessment	The study groups were not significantly different regarding treatment effect for these counts
Aydinlik S, Lachnit-Fixson U, Lehnert J. (1986) Reduced estrogen ovulation inhibitor in acne therapy Double-blind study comparing Diane-35 to Diane [Ostrogenreduzierter ovulationshemmer zur aknetherapie.]. *Fortschritte derMedizin* 1986;104:547–50.	Multicenter observational trial in 8 European countries. **Double blind** but no mention of who was blinded.	CPA 2 mg +EE 35 µg vs CPA 2 mg + EE 50 µg	**N=425** women of reproductive age with mild to moderate acne and seborrhea.	9 treatment cycles	Healing or improvement of acne cases from baseline	No abstract available but analysed in Cochrane : the two groups were not significantly different in acne outcomes and discontinuation rates: 59.17% (Diane 35) vs 55.55% (Diane 50) women with healed or improved facial acne lesions at cycle 9
Vartiainen M, de Gezelle H, Broekmeulen CJH (2001) Comparison of the effect on acne with a combiphasic desogestrel-containing oral contraceptive and a preparation containing cyproterone acetate Eur J Contracept Reprod Health Care 6 (2001) 46-53	open, randomized	CPA 2 mg + EE 35 µg vs Gracial[4]	**N=172** 88 vs 84 women with mild to severe acne	6 cycles	Number of acne lesions: comedos, papules, pustules, nodules, subjective and objective scores.	Number of lesions deceased significantly in both groups without significant differences between the groups.
Dieben T, Vromans L, Theeuwes A, Coelingh Bennink HJT (1994)	Multicenter trial in 4 European	DIANE 35 vs biphasic	**N=183** women aged 18 to 35	Washout period of 2	Acne lesion counts. Photograph assessment	Number and severity of lesions was reduced

The effects of CTR-24, a biphasic oral contraceptive combination, compared to Diane-35 in women with acne Contraception 50 (1994) 373-382	countries. Open trial except that photograph assessor was blinded.	desogestrel-EE combination[4]	years with at least 5 facial acne lesions.	months for hormonal contraceptives and 4 weeks for anti-acne medication. 4 treatment cycles.	using modified Burke and Cunliffe grades (“Grade 0” no comedos, papules, pustules or nodules; “Grade 1” comedos only; “Grade 2” papules, no nodules, no pustules; “Grade 3” pustules, no nodules; “Grade 4” nodules)	significantly in both groups without differences between the groups.
Fugere P, Percival-Smith RKL, Chir B, Lussier-Cacan S, Davignon J, Farquhar D (1990) Cyproterone acetate/ethinyl estradiol in the treatment of acne. A comparative dose response study of the estrogen component Contraception 42,2 (1990) 225-234	**Double blind randomized**	DIANE 35 vs DIANE (50)[1]	N=62 37 vs 25 women with moderate to severe acne	12 cycles	Different types of acne assessed using the Cook's method	Significant improvement of all types of acne in both groups

Efficacy Data of Diane 35 in acne (Bayer submission only)

Other references submitted by Bayer	Type of Study	Study Medication	Study Population	Observation	Clinical Parameters	Results
Clinical Study Report No A28501 (2006) Multicenter, double-blind, double-dummy, randomized parallel group study to evaluate the safety and efficacy of 0.030mg ethinylestradiol/2mg dienogest for 6 treatment cycles in female patients with papulopustular acne in comparison to 0.035mg ethinylestradiol/2mg cyproterone acetate and placebo ***Id Palombo-Kinne (2009***)	multicenter, **double blind**, **randomized**	DIANE 35 vs Valette[10] vs placebo	**N=1308** 537 vs 525 vs 246 women with mild to moderate acne	6 cycles	number of acne lesions	Significant reduction in the total numbers of lesions in both groups under active treatment without major differences between the groups, both combinations were significantly more effective than placebo.
Clinical Study Report No A18566 (2004) Multicenter, double-blind, randomized parallel group study on efficacy of 0.035 mg ethinylestradiol/ 2mg cyproterone acetate and of 0.035 mg ethinylestradiol/ 2mg cyproterone acetate in combination with 10 mg cyproterone acetate in comparison to triphasic ethinylestradiol/ norgestimate over 6 cycles in women with acne papulopustulosa	multicenter, **double blind, randomized**	DIANE 35 vs DIANE 35 plus 10mg CPA vs Pramino[9]	**N=1004** 335 vs 337 vs 332 women with moderate to severe acne	6 cycles	number of acne lesions	Significant reduction in the total numbers of lesions in all groups without major differences between the groups.
Van Vloten WA, Haselen CW, van Zuuren EJ, Gerlinger CG, Heithecker R (2003) The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea Cutis 69 (2003) 1-14	**Double blind, randomized**	DIANE 35 vs Yasmin[8]	**N=125** 43 and 82 women with mild to moderate acne	9 cycles	number of acne lesions	Median total lesion count was reduced by 59% in the DIANE 35 group and by 63% in the Yasmin group, both medications reduced also sebum production and undesired hair growth.
Aydinlik S, Kaufmann J, Lachnit-Fixson U, Lehnert J (1990) Long-term therapy of signs of androgenization with a low-dosed antiandrogen-oestrogen combination Clinical Trials Journal 27,6 (1990) 392-402	multicenter observational	CPA 2 mg + EE 35 µg	**N=1161** women with mild to moderate acne, seborrhea, mild hirsutism	36 cycles	Documentation of symptoms according to severity and localization pregnancy rate	Success rates after 12 cycles: 91% facial acne 88% chest acne 90% back acne 2 pregnancies in 21.196 cycles.
Greenwood R, Brummitt L, Burke B, Cunliffe WJ (1985) Acne: double blind clinical and laboratory trial of tetracycline,	**randomized double blind**	DIANE 35 vs tetracycline	**N=92** women with acne	6 months	sebum excretion rate	68% improvement in acne score in tetracycline

oestrogen-cyproterone acetate, and combined treatment Brit Med J 291 (1985) 1231-1235		(500mg)				group; 82% in DIANE 35 group
Cavalli G, Fedele D, Zamberletti M, Marchini M, Vercellini P (1986) Clinical effects of a new monophasic oral contraceptive with antiandrogenic activity (SHB 209 AE) in 458 treatment cycles 1st Int Congress on Gynecological Endocrinology, Madonna di Campiglio 1986, Casterton Hall Parthenon 1986	open, uncontrolled	CPA 2 mg + EE 35 µg	**N=35** women with acne, seborrhea and hirsutism of varying degree	15 months	Clinical assessment	Success rates after 3, 6 and 12 months: - acne 37, 64, 71% - seborrhea 10, 18, 33% - hirsutism 0, 5, 22%
Kaiser E (1986) Klinische Erfahrungen mit Diane-35, dem zur Zeit niedrigst dosierten antiandrogen wirkenden Ovulationshemmer, bei leichten bis mittelstarken Androgenisierungserscheinungen der Frau Geburtsh Frauenheilk 46 (1986) 681-782	open, uncontrolled	CPA 2 mg + EE 35 µg	**N=144** women with moderate acne and seborrhea	12 months	Clinical assessment	Success rates after 6, 9 and 12 months: - facial acne 47, 68, 96% - décolleté 53, 73, 86% - back 49, 66, 89% - seborrhea hair 47, 58, 76% - seborrhea skin 55, 77, 82%.
DeCecco L, Capitano GL, Bertolini S, Croce S, Centonze A (1987) Clinical and metabolic effects of a new estrogen-antiandrogen low dose combination New Developments in Biosciences 3, Berlin, New York, Walter de Gruyter 1987, p167-173	open, uncontrolled	CPA 2 mg + EE 35 µg	**N=24** women with mild to moderate acne, seborrhea, hirsutism	6 cycles	Clinical assessment: unchanged, slightly improved, considerably improved	Definitely satisfactory therapeutic effect
Törek L, Gimes R, Aydinlik S (1990) Rezidivhäufigkeit von Akne und Seborrhoe nach der Behandlung mit einem antiandrogenen Kombinationspräparat Dt Derm 38,2 (1990) 166-172	open, uncontrolled	CPA 2 mg + EE 35 µg	**N=108** women with mild to severe acne and seborrhea	max 12 cycles	Clinical assessment of severity pregnancy rate	Success rates after 3, 6 and 12 cycles: - facial acne 19, 87, 97% - décolleté 20, 75, 97% - back 27, 84, 100% - seborrhea hair 53, 82, 94% - seborrhea skin 64, 97, 99% No pregnancy occurred in 1.184 cycles.
Erkkola R, Hirvonen E, Luikku J, Lumme R, Männikkö H, Aydinlik S (1990) Ovulation inhibitors containing cyproterone acetate or	open, randomized	DIANE 35 vs Marvelon[3]	**N=162** 83 vs 79 women with	9 months	Clinical assessment: Symptoms not	Therapeutic success after 9 cycles was significantly better in the DIANE 35

desogestrel in the treatment of hyperandrogenic symptoms Acta Obstet Gynecol Scand 69 (1990) 61-65			mild to severe acne, seborrhea, hirsutism		present, mild or severe pregnancy rate	group: facial acne 81 vs 63% décolleté 86 vs 78% back 83 vs 82, % No pregnancy occurred in 658 DIANE 35 cycles.
Vegetti W, Testa G, Maggioni P, Motta T, Falsetti L, Crosignani PG (1996) An open randomized comparative study of an oral contraceptive containing ethinyl estradiol and cyproterone acetate with and without the GnRH analogue Goserelin in the long-term treatment of hirsutism Gynecol Obstet Invest 41 (1996) 260-268	multicenter, randomized	DIANE 35 vs DIANE 35 plus Goserelin[5]	**N=50** 26 vs 24 women with hirsutism and acne	12 cycles plus 6 cycles follow up	Subjective and objective evaluation of hair growth, mean hair diameter, visual assessment of acne	At least partial success in 95% of all patients with no significant differences between groups, decrease of hair diameter in the DIANE 35 group -14.5%; in the Goserelin group -20% all but one women with acne responded to the treatment in both groups.
Falsetti L, Ramazzotto F, Rosina B (1997) Efficacy of combined ethinylestradiol (0.035mg) and cyproterone acetate (2mg) in acne and hirsutism in women with polycystic ovary syndrome J Obstet Gynaecol 17,6 (1997) 565-568	open, uncontrolled	CPA 2 mg + EE 35 µg	**N=82** women with polycystic ovary syndrom, acne and hirsutism	48 cycles	number of acne lesions, assessment of hirsutism by Ferryman-Gallwey score	Acne resolved in all women within 24 cycles, mild and moderate hirsutism resolved within 48 cycles, severe hirsutism changed to mild or moderate in most of the cases.
Gollnick H, Albring M, Brill K (1998) The efficacy of oral cyproterone acetate in combination with ethinyloestradiol in acne tarda of the facial type J Derm Treatm 9 (1998) 71-79	open, multicenter, uncontrolled	CPA 2 mg + EE 35 µg	**N=890** women with grade I-IV facial acne according to Plewig and Kligman, the majority had acne tarda.	6 cycles	Number of acne lesions, assessment of seborrhoea and hirsutism	Good or very good reduction of acne lesions of >50% in 83% of the women after 6 cycles similar in all grades, reduction of seborrhoea and hirsutism
Clinical Study Report No AI58 (1999) A multicenter, double-blind, randomized comparative study on the therapeutic efficacy of SH D 592 E and SH D 592 B (Diane-35 plus 7 placebo tablets) in women with acne vulgaris for 9 months	Multicenter, Double-blind, randomized	CPA 2 mg + EE 35 µg vs 2mg CPA plus 0.02mg EE	**N=149** 51 vs 98 women with facial acne	9 cycles	Number of acne lesions	Significant reductions of the number of lesions in both groups without differences between groups

Clinical Study (1997) Report No13546	multicenter, **double blind, randomized**	DIANE 35 vs Valette[10]	**N=35** 18 vs 17 women with acne of grades 1-3	6 cycles	Clinical assessment by the investigators, photographic documentation, skin biopsies.	Significant reductions of acne and the sebaceous gland area in both groups without statistically significant differences between the groups

1 Diane 50: 2mg cyproterone acetate plus 0.05mg ethinylestradiol
2 Microgynon: 0.15mg levonorgestrel plus 0.03mg ethinylestradiol
3 Marvelon: 0.15mg desogestrel plus 0.03mg ethinylestradiol
4 Gracial: biphasic combination with 0.025mg desogestrel plus 0.04mg estinylestradiol for 7 days and 0.125mg desogestrel plus 0.03mg estinylestradiol for 15 days with a 6 day pill free period
5 Goserelin: GnRH analogue Zoladex 3.6mg
6 Triptorilin: GnRH analogue Decapeptyl 3.75
7 MPA: Medroxyprogesterone acetate
8 Yasmin: 3mg drospirenone plus 0.03mg ethinylestradiol
9 Pramino: triphasic combination of 0.18mg norgestimate plus 0.035mg ethinylestradiol for 7 days, 0.215mg norgestimate plus 0.035mg ethinylestradiol for 7 days and 0.25mg norgestimate plus 0.035mg ethinylestradiol for 7 days
10 Valette: 2mg dienogest plus 0.03mg ethinylestradiol

Diane 35 contraceptive effect

Diane 35 is the combination of anti-androgen, cyproterone acetate (2 mg or 2000 µg) and of estrogen, ethinylestradiol (35 µg) also named Co-cyprindiol 2000/35 in some countries.
Cyproterone acetate is a synthetic derivative of 17-hydroxyprogesterone, and acts as an anti-androgen which explains its activity in acne. In addition due to its composition, it is mentioned in the SmPC that Diane 35 inhibits ovulation.

In 1999 in response to the French Agency request to submit data to evaluate the contraceptive effect of Diane 35 due to a large misuse, Bayer provided an observational study[6] that was considered inadequate for granting a broader indication labelled as follows: "*"Treatment of acne in women **seeking or accepting a contraception.** The efficacy is moderate and only observed after several months of treatment."*

The purpose of this observational Aydinlik study (1990) was to assess the effects of Diane 35 on signs of androgenisation (acne, hyperseborrhea, hirsutism) and as a contraceptive. This was an uncontrolled open, multicenter phase III clinical trial performed in 6 countries (Austria, France, Germany, Italy, Hungary and the Netherlands) that analyzed data between 1984 and 1988 on 1161 women with mild to severe signs of androgenisation i.e. during 21196 cycles.
Based on this study, Bayer presented a Pearl Index value of 0.12 (non corrected Pearl Index) with an 95%CI of 0.44. The French Agency considered that these data were not sufficient to cover the misuse and to extend the indication of Diane 35.

In 2001 in response to the French Agency request for the review of benefit/risk of Diane 35, based on the same Aydinlik, study Bayer submitted a new Pearl Index value re-calculated according to the current European guidance on steroid contraceptives in women.
As the underlying clinical trial Aydinlik was performed many years before the current guidance was published, not all stipulations of the guidance could be followed. Therefore alternative estimates based on the completed EURAS observational trial performed by Dinger[7] were also provided by Bayer. However this study was not designed to determine the contraceptive efficacy of Diane 35 and nore did not match the European guidelines to assess contraceptive effect. The French Agency still considered these data not acceptable to extend the indication of Diane 35.

Therefore overall, the available efficacy data regarding the use of Diane 35 in contraception do not allow to establish its efficacy as a contraceptive. To ascertain its contraceptive effect, a well-designed study according to current European requirements should be performed. This explains the unfavourable opinion of the French Agency to amend and enlarge Diane 35 indication to the contraception as there are doubts that Diane 35 would not protect sufficiently women seeking contraception.

It is of note that as an estroprogestative drug, the SmPC of Diane 35 has been amended in 1995 and 2011 to introduce statements on the anti-ovulation effect due to the class-effect:

- in section 4.2:

"In case of incorrect administration:
When the anti-ovulation effect of Diane 35 is sought, one missed tablet exposes to a risk of pregnancy. If a tablet has been missed within 12 hours of the usual time, a single tablet should be taken as soon as possible and the treatment should be continued as usual.
If a tablet has been missed for more than 12 hours after the usual time, the anti-ovulation effect is not maintained and the omitted tablet should be taken as soon as possible and the treatment should be continued as usual till the end of the blister of 21-tablet. Additional contraceptive precautions are required (condoms, spermicides…) till the next 21-tablet blister is taken including during the tablet-free intervall."

[6] S. Aydinlik and al. Long-term therapy of signs of androgenisation with a low-dosed antiandrogen-oestrogen combination. Clinical trials journal 27,6 (1990) 392-402
[7] The safety of a drospirenone-contianing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contraception 75 (2007) 344-354.

Besides in 2004, in collaboration with the French Agency (ANSM) and the National Institute for Prevention and Health Education (INPES), the French National Authority for Health (HAS) published recommendations for clinical practice named "Strategies of the choice of contraceptive methods in women".

This guideline reminds that "products such as Diane 35 and its generics have not been granted the indication "contraception" and consequently their prescription with a contraceptive purpose, is under the own responsibility of the prescriber. Thus when the contraceptive and antiacneic effects are both sought, it is recommended to focus one of the pills that have the double indication "contraceptive and antiacne" (i.e. Tricilest and Triafemi for mild and moderate acne)."

Analysis of fatal cases recorded in the French safety database

Up to January the 21st 2013, 8 fatal cases (all causes) have been recorded in the National Pharmacovigilance Database (NPVD) since 1987: 6 cases related to Diane 35 and 2 cases related to a generic.
In these 8 cases, 1 case concerns a drug exposure during pregnancy reporting a congenital hernia leading to a pregnancy interruption. This case has been excluded for the analysis.

Analysis of the 7 remaining cases

In these cases, the main cause of death reported concerns thromboembolic venous adverse effects. Three deaths by embolism (or suspicion of pulmonary embolism) and one case of cerebral thrombosis were found.
(Of note, one case of suspicion of embolism was not correctly coded and thus has not been retrieved using the SMQ request thromboembolic adverse events).

For 3 cases of pulmonary embolisms, Diane 35 is reported as the only drug administered in 2 cases. The last case of pulmonary embolism reports a concomitant administration of Diane 35 with an herbal medicine, including green tea, and a death in a situation of hepatic failure.
One case out of these 3 cases mentions a history of pulmonary embolism but it is contradictory with the narrative of the case.

The case of cerebral thrombosis is poorly documented.

Concerning these 4 cases, the causal relationship between thromboembolism effect reported and Diane 35 cannot be excluded.

The three other fatal cases describe:

- a 42 -year-old woman with AIDS experienced hepatic encephalopathy. She was also treated by co-suspect treatments such as antiretroviral drugs (atazanavir, ritonavir and emtricitabin/tenofovir disoproxil) as well as cyproterone acetate.
- a 24 year-old woman developed a cardiomyopathy with several possible aetiologies such as genetic or viral also treated by desogestrel/ethinylestradiol, isotretinoin, and amphotericin B. The death occurred after a decompensation following a secondary infection.
- a 28 years old woman developed a bile duct carcinoma. Patient's medical history included two courses of treatment by Diane and cyproterone acetate and died 4 years after the end of the treatment. Of note cholangiocarcinoma is not known to be hormone-dependent.

For these three cases, the underlying diseases seem to have played an essential role in the death reported.

Vascular safety of Diane 35

1/ Data issued from literature (COC + Diane / Denmark /1995-2009)

- **Venous thromboembolic risk of oestroprogestatives**

Lidegaard[8] published in 2011 a Danish historical registry based cohort study issued from 4 registries in 1.2 million non-pregnant Danish women aged 15-49 years old with no history of thrombotic disease and followed from January 2001 to December 2009.

The main outcome measures were the relative and absolute risks of first time venous thromboembolism.

Within 8 010 290 women years of observation, 4 307 first venous thromboembolic events were recorded.

Compared with non-users of hormonal contraception or Diane 35, the relative risk of confirmed thromboembolism in users of Diane 35 was 4.1 (95% confidence interval 3.37 to 4.99).

Concerning women without any oral contraception, the risk of venous thromboembolic adverse events (VTAE) is 3.7 cases for 10 000 women followed during 1 year.
Concerning women receiving a COC from 2nd generation, this risk is increased **twofold**:
RR = 1.57 - 2.56 [0.84-2.92].
Concerning women receiving a COC of 3rd or 4th generation containing drospirenone, this risk increases fourfold:
RR = 4.21-4.47 [3.63-5.11].
Concerning women receiving Diane 35, this risk also increases **fourfold**:
RR = 4.10 [3.37-4.99].

The repartition for VTAE in the Cohort is as follows:
- 63.6 %: deep vein thrombosis
- 26.2 %: pulmonary embolism
- 10.2 % cerebral venous thrombosis, portal vein thrombosis, cava or renal (and not specified in 6.6 % of the cases).

[8] Øjvind Lidegaard et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423 doi: 10.1136/bmj.d6423

Exposure time, number of events of venous thromboembolism, crude incidence per 10 000 user years, and adjusted relative risk of venous thromboembolism in current users of different oral contraceptives and hormone releasing intrauterine device with non-users as reference group

Group	Women years	No of events*	Crude incidence per 10 000 user years*	Adjusted relative risk† (95% CI)
Non-use	4 960 730	1812	3.7	1 (reference)
Progestogen with 50 µg ethinylestradiol:				
Norethisterone	6848	11	16.1	5.66 (3.12 to 10.3)
Levonorgestrel	23 691	31	13.1	3.54 (2.48 to 5.05)
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	10	3.7	1.57 (0.84 to 2.92)
Phasic levonorgestrel	105 970	89	8.4	2.28 (1.85 to 2.83)
Levonorgestrel combined	104 251	78	7.5	2.19 (1.74 to 2.75)
Norgestimate	267 664	165	6.2	2.56 (2.18 to 3.01)
Desogestrel	170 249	201	11.8	4.21 (3.63 to 4.87)
Gestodene	668 355	738	11.0	4.23 (3.87 to 4.63)
Drospirenone	286 859	266	9.3	4.47 (3.91 to 5.11)
Cyproterone	**120 934**	**109**	**9.0**	**4.10 (3.37 to 4.99)**
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	322	6.8	3.26 (2.88 to 3.69)
Gestodene	472 118	321	6.8	3.50 (3.09 to 3.97)
Drospirenone	23 055	23	10.0	4.84 (3.19 to 7.33)
Progestogen only:				
Norethisterone	44 168	9	2.0	0.56 (0.29 to 1.07)
Desogestrel	29 187	6	2.1	0.64 (0.29 to 1.42)
Levonorgestrel releasing intrauterine device	155 149	55	3.5	0.83 (0.63 to 1.08)

*Events are venous thromboembolisms.
†Adjusted for age, year, and level of education.
Table extracted from Lidegaard 2011

- **Arterial thromboembolic risk of oestroprogestatives**

Lidegaard[9] published in 2012 a Danish historical registry based cohort study issued from 4 registries in non-pregnant Danish women aged 15-49 years oldwith no history of thrombotic disease and followed from January 2001 to December 2009.

The main outcome measures were the relative and absolute risks of first time arterial thromboembolism.
In 14 251 063 women-years of observation, 3 311 thrombotic strokes (21.4 per 100 000 person-years) and 1 725 myocardial infarctions (10.1 per 100 000 person-years) occurred.

[9] Øjvind Lidegaard et al. Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception. N Engl J Med 2012;366:2257-66.

Compared with non-users of hormonal contraception or Diane 35, the relative risks of confirmed arterial thromboembolism in users of Diane 35 were 1.4 (95% confidence interval 0.97 to 2.03) for thrombotic stroke and 1.47 (95% confidence interval 0.837 to 2.61) for myocardial infarction.

Incidence Rates and Adjusted Relative Risks of Thrombotic Stroke and Myocardial Infarction among Users of Different Types of Hormonal Contraception, as Compared with Nonusers.*

Type of Hormonal Contraception	**No. of Person-yr**	**Thrombotic Stroke**			**Myocardial Infarction**		
		No. of Events	Incidence Rate *no. of events/ 100,000 person-yr*	Adjusted Relative Risk (95% CI)†	No. of Events	Incidence Rate *no. of events/ 100,000 person-yr*	Adjusted Relative Risk (95% CI)†
None	9,336,662	2260	24.2	1.00	1228	13.2	1.00
Ethinyl estradiol, 50 µg							
Norethindrone	43,234	9	20.8	1.27 (0.66–2.45)	11	25.4	2.74 (1.51–4.97)
Levonorgestrel	54,474	32	58.7	2.26 (1.59–3.20)	36	66.1	4.31 (3.09–6.00)
Ethinyl estradiol, 30 to 40 µg							
Norethindrone	126,984	28	22.1	2.17 (1.49–3.15)	14	11.0	2.28 (1.34–3.87)
Levonorgestrel	460,559	144	31.3	1.65 (1.39–1.95)	91	19.8	2.02 (1.63–2.50)
Norgestimate	453,536	78	17.2	1.52 (1.21–1.91)	28	6.2	1.33 (0.91–1.94)
Desogestrel	313,560	99	31.6	2.20 (1.79–2.69)	43	13.7	2.09 (1.54–2.84)
Gestodene	1,318,962	285	21.6	1.80 (1.58–2.04)	133	10.1	1.94 (1.62–2.33)
Drospirenone	286,770	52	18.1	1.64 (1.24–2.18)	18	6.3	1.65 (1.03–2.63)
Cyproterone acetate	**187,145**	**29**	**15.5**	**1.40 (0.97–2.03)**	**12**	**6.4**	**1.47 (0.83–2.61)**
Ethinyl estradiol, 20 µg							
Desogestrel	695,603	105	15.1	1.53 (1.26–1.87)	40	5.8	1.55 (1.13–2.13)
Gestodene	564,268	88	15.6	1.70 (1.37–2.12)	21	3.7	1.20 (0.77–1.85)
Drospirenone	23,056	2	8.7	0.88 (0.22–3.53)	0	0	0 (0.00–12.99)
Progestin only							
Norethindrone	85,874	28	32.6	1.35 (0.93–1.96)	9	10.5	0.81 (0.42–1.56)
Levonorgestrel	8,556	1	11.7	0.44 (0.06–3.12)	0	0	0 (0.00–35.01)
Desogestrel	29,185	9	30.8	1.37 (0.71–2.63)	4	13.7	1.46 (0.55–3.90)
Levonorgestrel IUD	184,875	45	24.3	0.73 (0.54–0.98)	31	16.8	1.02 (0.71–1.46)
Implant	24,954	3	12.0	0.88 (0.28–2.72)	3	12.0	2.14 (0.69–6.65)
Other							
Patch	4,748	2	42.1	3.15 (0.79–12.60)	0	0	0 (0.00–63.10)
Vaginal ring	38,246	12	31.4	2.49 (1.41–4.41)	3	7.8	2.08 (0.67–6.48)

* IUD denotes intrauterine device.

† Relative risks were adjusted for age, educational level, calendar year, and risk factors.

Table extracted from Lidegaard 2012

2/ Data from the French Pharmacovigilance database (Diane 35 & generics / France / since 1987)

- **Methodology of the Pharmacovigilance request**

Up to January 16th 2013, 127 cases concerning the embolic and thrombotic events (SMQ 20000081) for Diane 35 and its generics medicines are recorded in the National Pharmacovigilance Database since 1987 (date of MA of Diane 35 in France).
Of these 127 cases, 2 cases were excluded: one because it reported a disseminated intravascular coagulation and the second one because it reported a thrombotic thrombocytopenic purpura.
Of the 125 remaining cases, 113 cases concerned venous thromboembolic adverse events and mixed arterial/venous and 12 cases concerned arterial thromboembolic adverse events. They are described below.
The thromboembolic adverse events are listed in the current French Summary of Product Characteristics (SmPC).

- **Venous thromboembolic adverse effects**

Of the 113 cases of venous thromboembolic adverse events, 89 are attributed to Diane 35 and 24 cases to its generics.

Among the 113 cases retrieved, 110 reported venous thromboembolic adverse events and 3 reported mixed thromboembolic adverse effects (arterio-venous).

Analysis of the 113 cases

- Age

The age of women at the time of onset of the effect is specified in every case.
The mean age is 25 years old.
The median age is 24 years old [13 - 50 years old].
The distribution shows that 25 women are under the age of 18 years old and 6 women are aged of 40 years old and older.

- Weight

The data concerning the Body Mass Index (BMI) is recorded for 35 patients.
Mean BMI: 23.5
Median BMI: 21
Number of patients with a BMI between 25 and 28: 4 patients
Number of patients with a BMI > 28: 6 patients (BMI = 29/30/32/32/36/39)

- Indications

The indication is specified in 40 cases:

- 22 cases report a use for contraception,
- 14 cases report a use for acne,
- 2 cases report a use for acne and contraception,
- 1 case reports a use for hirsutism,
- 1 case reports a use for a dysmenorrhoea.

- Reported adverse effects

The diagnoses reported or mentioned for these 113 cases are:

- 65 cases of pulmonary embolisms with or without deep vein thrombosis including one case reporting a Budd-Chiari syndrome ,
- 38 cases of deep vein thrombosis,
- 10 cases of venous thrombosis NOS or superficial thrombosis.

- Time to onset (TTO)

The time to onset is specified for 72 of the 113 cases.
The mean TTO is of 749 days.

The median TTO is of 244 days [10 - 5856 days].
In 47 cases, the TTO is lower than or equal to 1 year (67 %).
Concerning the patients treated with Diane 35 (or its generics) over a very long period, we cannot estimate the accuracy of the data because there is a possibility of stop and restart of the treatment for several reasons (medical, personal…).

- Risk factors

An analysis of the risk factors, when identified in the observations, shows that out of the 113 reported cases:

- 54 women did not present identified risk factor (including 5 patients who had a complete research of the factors which was negative and 10 cases not documented or poorly documented) ;
- 27 women presented at least one haemostatic disorder whereas 32 women had no haemostatic disorder (haemostatic risk factors research was not performed for 54 women) ;
- 40 women presented at least a "clinical" risk factor (age > 40 years, overweight with BMI over 25, direct personal or family medical histories, co-suspect medication, or immobilization).

In total, 59 women were reported to have at least 1 risk factor ("clinical" or haemostatic).
Moreover, 9 women have at least 1 clinical and 1 haemostatic risk factor.
The "clinical" risk factors are considered avoidable as they can be identified before the occurrence of the thromboembolic adverse effects whereas haemostatic risk factors are in most cases discovered after occurrence of the effect.

- Associated drugs

In cases reported, Diane 35 (or its generics) was:

- the only drug for 82 patients,
- associated with cyproterone acetate for 12 patients,
- associated with isotretinoin for 5 patients,
- associated with a drug known to be linked with an increased thrombosis risks (estradiol, adalimumab, tranexamic acid, carbamazépine for 5 patients).

For cases in which Diane 35 (or its generics) was associated with isotretinoin, Diane 35 (or its generics) seems to have been used as a contraceptive to be protected from the teratogenic risk of isotretinoin which is inappropriate due to the lack of efficacy data for Diane 35 as a contraceptive drug and because of .

- Outcome

For the 113 cases, outcomes were reported as:

- recovered without sequel in 68 cases,
- recovered with sequel in 7 cases,
- subject not yet recovered in 30 cases,
- unknown in 5 cases,
- fatal in 3 cases.

<u>Analysis of three reported fatal cases</u>

- Age
  - a 42-year-old woman (occurrence in 1990) treated with Diane 35 (poorly documented case),
  - a 24-year-old woman (occurrence in 1995) treated with Diane 35,
  - a 18-year-old woman (occurrence in 2007) treated by Holgyeme.

- Indications

The indication is provided in one of the 3 cases (case reported with Diane 35 and that occurred in 1995) and specifies a use as a contraceptive. The indication is not provided for the two other cases.

- Reported adverse effects

The effects reported in these 3 cases are:

- a cerebral thrombosis for the 42-year-old woman,
- a pulmonary embolism, a deep phlebitis with loss of consciousness for the 24-year-old woman (following a pelvic phlebitis),

- a pulmonary embolism for the 18-year-old woman.

These cases are poorly documented.

- Time to onset

For the case of the 24-year-old woman, the time to onset is 17 months, and for the case of the 18-year-old woman, the time to onset is 6 months. It is unknown for the last case.

- Risk factors

The 24-year-old woman had a family medical history of pulmonary embolism.
The 18-year-old woman had no direct medical history.

- Associated medication

No associated treatment for these 3 cases.

Conclusion for the venous and mixted arterio-venous thromboembolic adverse events:
Of the 113 women who experienced venous and arterio-venous thromboembolic adverse effects, 25 women were aged 18 years or less (22.1 %). The indication was mainly reported as contraception (24 cases of the 40 cases reporting indication).

The majority of the reported venous thromboembolic adverse events are pulmonary embolisms associated or not with deep venous thrombosis (65 cases on 113). These thromboembolic adverse events are listed in the current French Summary of the Characteristics of the Product.
The time to onset is less than 1 year for 67 % of the cases (47 cases). Concerning the venous and arterio-venous thromboembolic adverse events, 59 cases of 113 (52.2 %) were reported with identifiable risk factors.
Consideration of these risk factors could have prevented the occurrence of the venous thromboembolic adverse events in 40 women (35.4 % of the cases).

- **Arterial thromboembolic adverse events**

Of the 12 cases of arterial thromboembolic adverse events, 11 concern the Diane 35 and 1 concerns its generic (Minerva).
Three cases were not included in the global analysis since the arterial nature of the thrombosis was uncertain. They are nevertheless described at the end of the section.

So, the analysis concerns 9 cases.

Analysis of the cases

- Age

The age of the women at the time of occurrence of the effect is specified in every case.
The mean age is 31 years old; the median age is 30 years old [19 - 44 years]. The distribution shows that 6 women are aged from 19 to 34 years old and 3 aged from 39 to 44 years old.

- Indications

The indication is specified in 7 cases:
- 5 cases reported an indication in contraception,
- 1 case reported an indication in hyperpilosity,
- 1 case reported an indication in acne and contraception.

- Reported adverse effects

The diagnoses reported or mentioned for these 9 cases are:
- 3 cases of stroke among which 2 are clearly identified and confirmed in the MRI,
- 2 cases of transient ischemic attack
- 3 cases reporting symptoms suggestive for an CVA (choreoathetoid movements, cephalgia, hemiparesis, blindness for one case ; paralysis, ictus, paralysis of the soft palate, deviation of the uvula for the other one),
- 1 case of myocardial infarction.

In 3 cases, it is specified that a whole search has been completed but no aetiology has been found.

- Time to onset

The time to onset is specified for 4 of the 9 cases.
The mean time to onset is 3 591 days; the median time to onset is 3 477 days [90 - 7 320 days].
It is important to note that among 4 cases for which the time to onset is specified, one woman temporarily interrupted her treatment 10 years ago for a pregnancy. Besides, for one of the women, the effect occurred within 3 months after initiation of treatment; others occurred within at least 4 years.

- Risk factors

A research for identified risk factors in the observations showed that among the 9 cases:
- 3 women did not present risk factor,

- 4 women presented a risk factor due to the presence of a concomitant disease or medical histories (foramen ovale, hypertension, Fabry's disease or migraine),
- 3 women presented an aged-related risk factor (39 years),
- 2 women presented tobacco as a risk factor
- 1 woman presented a risk factor related to family history (father died from pulmonary embolism and mother underwent 3 aorto-coronary bypass procedures).

It should be noted that, with the exception of the case of myocardial infarction in a 44-year-old female smoker with hypertension, a relevant family history, and a case of transient ischemic attack for a 39-year-old patient with a history of migraine, none of the women had more than one identified risk factor at the same time.

- Associated medications

With the exception of one case of combined treatment with Diane 35 and cyproterone (the first for contraception and the second for hirsutism), ethinylestradiol/cyproterone combined therapy is always the only medication reported.

- Outcome

For the 9 cases, the following outcomes were notified for the reported effect(s):

- recovered without sequel in 5 cases,
- recovered with sequel in 3 cases,
- patient not yet recovered in 1 case.

<u>Analysis of the 3 cases for which the arterial nature of the thrombotic event is uncertain</u>

- Age

The age of the women at the time of onset of the event is specified in all cases. The mean age is 27 years; median age is 23 years [20 - 39 years].
The distribution shows that 2 women are aged 20 to 23 years old, and 1 woman 39 years old.

- Indications

The indication is stated in 2 out of these 3 cases, and mentions use for contraception.

- Reported adverse effects

The events reported in these 3 cases are:

- ictus and cerebral hyperaemia in a 39-year-old woman,
- tension headaches, paresis of the right arm, lasting 20 minutes, in a 20-year-old woman (clinical examination and brain CT scan unremarkable),
- ictus in a 23-year-old woman (aetiological differential diagnosis: patent *foramen ovale*).

It should be noted that 2 of the cases are poorly documented.

- Time to onset

The time to onset is reported in all 3 cases. It was 2 years in 2 cases and 3 years in 1 case.

- Presence of risk factors

Investigation for identified risk factors showed that within the 3 cases analysed:

- 1 woman presented protein S deficiency and antiphospholipid antibodies,
- 1 woman presented a risk factor related to smoking.

The presence of patent *foramen ovale* in the third case is unclear.

- Associated medication

With the exception of one case of combined therapy with Diane 35 and cyproterone acetate, ethinylestradiol/cyproterone combined therapy is the only medication reported for all cases.

- Outcome

For the 3 cases, the following outcomes were reported:

- recovered without sequel in 1 case,
- recovered with sequel in 1 case,
- patient not yet recovered in 1 case.

Conclusion:
Of the 12 women who presented arterial thromboembolic effects, 6 women were aged from 19 to 34 years old. When reported, the indication for uses was mainly contraception.

The majority of adverse effects reported correspond to stroke, transient ischaemic attack, or cases with associated stroke symptoms (8 out of 9 cases). These adverse effects are listed in the Summary of Product Characteristics.
Time to onset was poorly documented, and was greater than 4 years in 3 out of the 4 cases reported.

Thrombotic events may have been avoided if risk factors, which are reported for 6 cases on 9 and known prior to onset, had been taken in account.

3/ Data of the Periodic Safety Updated Reports (PSURs 2008-2012) on the thrombotic risk (Diane 35 & Minerva & Androcur & Femilar / worldwide / 2008-2012)

The last 4 PSURs of the products Diane 35 and Minerva covering the period from October 13th, 2008 to May 31st, 2012 were examined. These two products are marketed by the same laboratory and cover 44 % of market shares. The safety data presented in these PSURs were thus considered as representative of the association.

The summary report covering the period from October 13th, 2008 till May 31st, 2012 was also taken into account. These reports also concern cyproterone in the dosages in 50 and 100 mg and Femilar (association of cyproterone acetate and estradiol valerate marketed only in Finland).

- **Information on the product**

The product Diane 35 has got a marketing authorisation since 1987 and is at present authorised in 126 countries in the treatment of the androgenic problems at the women: acne (nodulo-cystic forms and papulo-pustular), androgenic alopecia and moderate forms of hirsutism.

The exposure corresponds to 15 million treatments / years over the 4 years of the report. 644 medically confirmed cases were reported over this period including 286 serious cases. Globally 3299 cases were notified in the world since the first marketing.

The Company Core Data Sheet (CCDS) of Diane 35, which is the source document for the MAH, was modified to improve the information regarding the venous thromboembolic risk. These modifications were applied in France on October 7th, 2011.

The marketing authorization holder concluded after analysis that the benefit / risk balance of its products remained favourable.

Besides it is of note that during the period of these PSURs, modifications for safety reasons concerned cyproterone and its potential risk of meningioma and hepatotoxicity. Meningioma is observed with important doses and during prolonged treatments. Hepatotoxicity is also dose dependant with a risk of fulminant hepatitis for doses beyond 100 mg.

The analysis of the NPVD data confirmed that the most worrisome adverse effects of Diane 35 are the thrombotic adverse events (arterial or venous), data from PSURs were assessed in this perspective only.

- **Method**

PSURs 17, 18, 19 and 20 covering the period from October 13th, 2008 till May 31st, 2012 were analysed. In these reports, the following adverse effects' approach has been taken into account:

- data relative to the deaths linked with a thrombotic effect,
- cases of thrombosis developed by the firm,
- all the medically confirmed serious cases considered as listed or not in the vascular System Organ-Class (SOC),
- all cases of thrombotic effects reported in line listings and classified in other SOC.

The cases of superficial phlebitis were excluded.

Finally, 145 cases reporting thrombotic adverse effects were identified. Of these 145 cases, 28 cases were reported in France including 15 cases reported by the French Health Authorities. These 15 cases were also included in the synthesis presented above on data coming from the French pharmacovigilance database.

- **Venous thromboembolic adverse effects**

Of the 145 cases reported with thromboembolic adverse events, 125 of them (85 %) are venous events divided into:

- 78 pulmonary embolisms (62.4 % of the venous adverse events). In 26 cases the description of the case mentioned an associated deep vein thrombosis,
- 18 deep cerebral thrombosis (14.4 % of the venous adverse events),
- 29 "isolated" deep vein thrombosis, i.e. not complicated with pulmonary embolisms (23.2 % of the venous adverse events). Among the described adverse effects, two axillary thrombosis and one Budd-Chiari syndrome were reported.

Among these cases, the outcome was reported in 74 cases, as:
- favourable in 59 cases (80 % of the cases),
- with sequel in 5 cases (7 % of the cases),
- fatal outcome in 10 cases (13 % of the cases). Death occurred in 9 cases following a pulmonary embolism and 1 death following a cerebral thrombosis.

The age of the women is reported in 112 cases:
- 90 are less than 35 years old (80 %),
- 14 are between 35 and 40 years old (12.5 %),
- 8 are over 40 years old (7.5 %).

It is to note that the age of 35 years or above is considered as a risk factor for the thromboembolic risk and this finding should be carefully considered when prescribing Diane 35 (and its generics).

The time to onset is reported in 70 cases. The median time is of 4 months (1 month to 20 years). In 61 cases (87 % of the cases), the adverse effects occurred during the first year of treatment.

For 15 patients (12 % of the cases), risk factors besides age were identified:
- 3 cases of haemostatic abnormalities (1 homozygous mutation of the factor II for a person presenting family medical history of venous thrombosis, 1 genetic MTHFR mutation, 1 case not documented). The diagnosis of haemostatic abnormalities is often discovered at onset of the event (risk factor identified afterwards).
- 11 cases reported an associated intake of another medicine which is identified by the marketing authorization holder as presenting a thromboembolic risk (5 cyproterone acetate, 1 natalizumab, 1 drospirenone/ethinyl estradiol, 1 olanzapine, 1 thalidomide, 1 méthylprednisolone, 1 not specified chemotherapy). Two of these patients had also an aged-related risk factor associated.
- 1 case of prolonged immobilization (flight).

35 patients (28 %) reported at least 1 risk factor; which should have been taken into account to propose another treatment for acne.

- **Arterial thromboembolic adverse events**

19 of 145 thrombotic adverse events are arterial effects (14 %) divided into:
- 15 strokes,
- 1 splenic infarction,
- 1 retinal infarction,
- 2 ischemic colitis (one of the patients presented haemostatic disorders concerning the protein S and the factor V and the other one was treated by interferon for a multiple sclerosis.

Among these cases, the evolution is reported for 11 cases, as:

- favourable in 6 cases (54 % of the cases),
- recovered in 5 cases (45 % of the cases).

No death was reported.

The age of the women is reported in 18 cases:

- 14 are less than 35 years old (78 %),
- 2 are between 35 and 40 years old (11 %),
- 2 are over 40 years old (11 %).

The time to onset is reported in 10 cases and the median is 4 months (from 1 month to 120 months).
For 5 patients ie 26 % of the patients, risk factors were identified:

- age over 35 years old in two cases. In one case, in addition to age as a risk factor, two other risk factors: tobacco and family medical history of cardiovascular disorder were reported. In another case the patient had a risk factor of haemostatic disorder (cf. ischemic colitis),
- age over 40 years in two cases,
- 1 with Fabry's disease

- **Conclusion on PSURs (2008-2012):**

The description of the cases reported in the last 4 PSURs confirms the safety profile of Diane 35 regarding the risk of occurrence of thrombosis, mainly venous thrombosis. The analysis of the time to onset (when reported) also indicates that the venous thromboembolic adverse events occurred at the beginning of the treatment, 50% of the cases within 4 months and 87 % of the cases during the first year of treatment. This highlights the need to closely monitor women being prescribed Diane 35 especially at the initiation of the treatment (or during the first year after restart of treatment after an interruption of more than 4 weeks).

Reported cases of venous thromboembolic adverse events seemed more serious and lead to a more often fatal outcome than what is expected based on the pharmaco-epidemiological data (1-2 % of death). The seriousness and the unusualness of these adverse effects in young women may explain that these cases are more notified than the non-complicated thromboembolic adverse events.

Finally, some of these thromboembolic adverse events are reported with "avoidable" risk factors whether they are venous or arterial. Indeed, the strict compliance to contraindications and the precautions for use of the SmPC would have allowed to avoid 33 out of 125 cases of venous thromboembolic adverse events and in 5 out of 19 cases of arterial thromboembolic adverse events (i.e. represents 26 % of cases of thromboembolic adverse events described in the 4 PSURs). These risk factors are easily screened during the interrogation or the clinical examination. It is to note that the cases reported in the PSUR were briefly documented and lead to think that the consideration of the other risk factors not mentioned (such as the BMI) would allow lowering the risk.

To conclude, the review of cases registered in the French Safety Database since 1987 and in the PSURs since 2008, emphasizes the occurrence of thromboembolic adverse events reported with Diane 35, including cases with a fatal outcome. This points out the necessity to search for risk factors before the prescription, which is not adequately performed despite being mentioned in the product information.

Benefit/risk review

- **Anti-acneic effect**

Acne is a common, benign and transient skin disorder which management includes hygiene measures possibly associated to local and oral medications.

In 2012, the Cochrane review concluded that COCs reduce acne lesion count, severity grades and self-assessed acne in placebo-controlled trials and should be considered for women with acne who also want an oral contraceptive. Although COCs containing cyproterone have been traditionally used for acne treatment, little evidence shows superiority over other progestins.

There is no direct comparison between Diane 35 and other acne treatments, especially antibiotics or isotretinoine.

In France since 2007, it is recommended to use Diane 35 as a maintenance treatment of acne in women

- **Thromboembolic risk**

Diane 35 presents:

- a ***venous*** thrombotic risk comparable to the risk of 3rd generation COCs and 4th generation COCs containing drosperinone. In a large Danish cohort study in 2011, this risk over one year was assessed at 3.7 cases per 10 000 women not taking a combination of cyproterone acetate/ethinylestradiol (or COC), while the same risk was ***4 times higher*** in women taking a combination of cyproterone acetate/ethinylestradiol ;

- an ***arterial*** thrombotic risk comparable to the risk of 2nd-3rd and 4th generation COCs. In another large big Danish cohort study in 2012, this risk over one year was assessed at 2.42 cases for cerebrovascular accident and 1.32 cases for myocardial infarction per 10 000 women not taking a combination of cyproterone acetate/ethinylestradiol (or COC), while the same risk was ***1.4 times higher*** in women taking a combination of cyproterone acetate/ethinylestradiol.

Data from the French safety database and from PSURs confirmed the occurrence of cases of thromboembolic events, arterial and/or venous, including fatal cases, in patients exposed to Diane 35 or generics.

Based on the analysis of the French database, the French Agency estimates than about one quarter of accidents could have been avoided, if the thromboembolic risk factors had been taken into account.

- **Confusing use of Diane 35**

Diane 35 is a combination of one estrogen and one progestin, whose anti-ovulatory activity has not been validated with a Pearl index calculated according to required criteria.
In the French medical practice, this combination is currently and predominantly being used as oral contraceptive especially in young women. This use generates confusing medical messages.

Subsequently, the lack of demonstrated efficacy as contraceptive exposes women to a risk of unwanted pregnancy that is not estimated and not taken into consideration when prescribed. Its use also exposes women to a venous thromboembolic risk comparable to the risk of 3rd generation COCs and 4th generation COCs containing drosperinone, whereas no recommendation exists regarding Diane 35 use as second line oral contraceptive.

Moreover since Diane 35 is not a validated contraceptive, it cannot be used in women with acne who seek contraception, which represents a significant proportion of the concerned population. Thus prescribing Diane 35 means that other hormonal contraceptives cannot be prescribed without putting patients at risk

for oestrogen and/or progestin overdose. Besides in case of severe acne, Diane 35 should not be used concomitantly with isotretinoin, as isotretinoin treatment requires reliable, controlled protection against pregnancy. In summary the theoretical target population for Diane 35 in compliance with the product's MAs is very limited.

- **Benefit/Risk ratio of Diane 35**

The ANSM considers that the benefit/risk ratio related to Diane 35 (and its generics) is not favourable since the drug's modest efficacy as acne treatment cannot offset the risk of thromboembolic events and unwanted pregnancy.

This situation also presents a general public health concern regarding the need for all concerned women to be proposed a safe and effective contraception. The confusion results on the one hand from the acne indication and on the other hand from the composition of these medicinal products and their actual contraceptive use in clinical practice due to their similarity to oral contraceptives, despite the fact that their contraceptive efficacy has not been established. This confusion could spoil the confidence that women have in contraception in general, while a wide contraception accessibility remains a French government priority.