HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

The legally binding text is the original French version

OPINION

20 June 2012

GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 20 micrograms, coated tablets
Blister of 21 tablets, B/1 (CIP code: 379 354-4)
Blister of 21 tablets, B/3 (CIP code: 379 355-0)

GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 30 micrograms, coated tablets
Blister of 21 tablets, B/1 (CIP code: 379 350-9)
Blister of 21 tablets, B/3 (CIP code: 379 351-5)

Applicant: RANBAXY PHARMACIE GENERIQUES

gestodene 0.075 mg / ethinylestradiol 0.020 mg
gestodene 0.075 mg / ethinylestradiol 0.030 mg

List I

ATC code (2011): G03AA10

Date of Marketing Authorisation:
GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 20 micrograms: 30 May 2007 (national procedure)
GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 30 micrograms: 29 May 2007 (national procedure)

Reason for the review: Re-assessment of the actual benefit of third-generation oral contraceptives in response to a request by the Directorate-General for Health dated 27 December 2011.

Therapeutic indication:
“Oral hormonal contraception.”

The Transparency Committee has re-assessed the actual benefit of oral contraceptives containing desogestrel, gestodene or norgestimate in combination with ethinylestradiol at a dose of 15, 20, 30, 35 or 40 micrograms (termed third-generation). This re-assessment is based on the data contained in the appended report and on expert opinion.

1. Actual benefit (see appendix)

Access to contraception that is safe, effective and suitable for all women who choose to use it is a public health priority.

Such products are used to prevent unwanted pregnancies.

Taking into account the efficacy data (unchanged since previous Committee assessments), but with safety data having confirmed and quantified an increased risk of venous thromboembolic events compared with second-generation (containing norgestrel or levonorgestrel in combination with ethinylestradiol) and first-generation (containing norethisterone in combination with ethinylestradiol) oral contraceptives, the efficacy/adverse effects ratio must be considered to be low.

> Public health benefit
> Ensuring access to suitable contraception and reducing the frequency of voluntary terminations of pregnancy are public health objectives defined by the National Technical Group for the Definition of Public-Health Objectives (GTNDO).
> There is therefore a public health need, but the response to this need does not necessarily mean reimbursement of new oral contraceptives.
> On the basis of the available data, the impact in terms of any increase in contraceptive coverage brought about by reimbursing the costs of third-generation oral contraceptives could be offset by the increase in venous thromboembolic events in healthy women taking third-generation oral contraceptives compared with first- and second-generation oral contraceptives.
> Third-generation oral contraceptives are not therefore expected to benefit public health.

There are numerous alternatives to these contraceptives.

Following on from previous Transparency Committee Opinions, the new data that are available no longer allow third-generation oral contraceptives to be positioned as a second-line option.

In 2012 the Transparency Committee considers that, taking into account both the increased risk of venous thromboembolic events and the lack of demonstrated benefit in terms of clinical safety in women exposed to third-generation oral contraceptives compared with second- or first-generation oral contraceptives, the actual benefit of the proprietary medicinal products GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 20 micrograms and GESTODENE/ETHINYLESTRADIOL RANBAXY 75 micrograms / 30 micrograms must be regarded as **insufficient** for reimbursement by National Health Insurance.

2. Transparency Committee recommendations

The Transparency Committee does not recommend continued inclusion[1] on the list of medicines reimbursed by National Health Insurance in the indications and at the dosage in the Marketing Authorisation.

Medical, Economic and Public Health Assessment Division

[1] This also means that the Committee does not recommend listing unlisted proprietary medicinal products included in this assessment.

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

Third-generation oral contraceptives

Re-assessment

APPENDIX

June 2012

Medical, Economic and Public Health Assessment Division

CONTENTS

BACKGROUND AND INTRODUCTION

The HAS Transparency Committee (TC) evaluates medicinal products that have been granted marketing authorisation (MA) when the company marketing them would like them to be included in the list of medicines reimbursed by National Health Insurance (article L.162-17 of the Social Security Code) and/or on the list of medicines approved for use by hospitals (article L.5123-2 of the Public Health Code) or on request.

The TC is a scientific body made up of doctors, pharmacists and specialists in methodology and epidemiology. Its objectives include:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospitals, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer over treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant, independent scientific information on the products.

These objectives are defined in the Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.
According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76, R. 161-85 of the Social Security Code and articles L. 5123-2 and L. 5123-3 of the Public Health Code, the TC Opinion specifies the actual benefit and improvement in actual benefit provided by the medicinal product. This assessment is carried out on the basis of a critical analysis of the scientific literature according to evidence-based medicine databases and expert opinion. The medicines are re-assessed in the indications and at the dosages in the Marketing Authorisation.

I. Subject of the request

Following the publication of studies confirming and quantifying the increased risk of venous thromboembolic events associated with the use of third-generation combined oral contraceptives compared with first- and second-generation products, the Directorate-General for Health submitted a request to the Transparency Committee on 27 December 2011 concerning "the assessment of third-generation oral contraceptives, in particular the assessment of the AB of these treatments, their therapeutic benefit and the parameters for their reimbursement."

The oral contraceptives covered by this re-assessment, termed third-generation, are proprietary medicinal products containing one of the following three combinations of active substances:

- desogestrel/ethinylestradiol,
- gestodene/ethinylestradiol,
- norgestimate/ethinylestradiol.

The ethinylestradiol dosage is 15, 20, 30, 35 or 40 micrograms, depending on the product.

This assessment concerns 53 third-generation contraceptive products (46 that are being re-assessed, see Table 1, and 7 undergoing listing, see Table 2), which correspond to all proprietary medicinal products assessed by the Transparency Committee since 2002 for which an application for inclusion on the list of medicines reimbursed by National Health Insurance has been made.[2]

It should be noted that the status of the proprietary medicinal products covered by this re-assessment is heterogeneous as regards reimbursement; some of them are reimbursable and others are not.

Of the 50 third-generation proprietary medicinal products currently on the market (for which an application for inclusion on the list of medicines reimbursed by National Health Insurance may or may not have been made), only 23 are currently reimbursable.[2]

[2] These figures are likely to change as products are launched or taken off the market or have their Marketing Authorisation withdrawn.

II. Summary of previous Committee opinions on third-generation oral contraceptives

II.1 Applications for inclusion on the list in July 2002 and February 2003

The Transparency Committee assessed some third-generation oral contraceptives in 2002 during the application for their inclusion on the list of medicines that can be dispensed to outpatients by retail pharmacies and on the list of medicines approved for use by hospitals.
The conclusions of the Committee were as follows:

- Contraceptive efficacy

There was no difference in effectiveness in preventing pregnancy between second- and third-generation combined contraceptives.

- Safety and adverse effects
  - The relative risk of venous thromboembolism of third-generation combined contraceptives versus second-generation is between 1.5 and 2.
  - It is not possible to conclude any difference between third- and second-generation combined contraceptives in terms of the risk of arterial thrombosis.

In the absence of adequate data, no distinction can be made between third-generation combined contraceptives containing less than 30 µg of ethinylestradiol and other third-generation combined contraceptives.

As regards the Opinion on the proprietary medicinal product CILEST: “norgestimate is considered in France to be a third-generation progestogen. Because of the lack of adequate data on this progestogen, no distinction can be made from other third-generation progestogens. This means that the special warnings concerning combined contraceptives containing norgestimate are identical to those proposed for other third-generation combined contraceptives containing gestodene or desogestrel.”

For these proprietary medicinal products, the Committee concluded that there was a substantial AB, but no IAB compared with second-generation contraceptives, and recommended that they be included on the list of medicines that can be dispensed to outpatients by retail pharmacies and on the list of medicines approved for use by hospitals.
The Committee had requested additional information:
“This Opinion is to be reviewed no later than 24 months from now. On the basis of the available data, it is very difficult to assess the status of this proprietary medicinal product in relation to its alternatives. For this review, the pharmaceutical company must provide data that permit assessment of the tolerance of this proprietary medicinal product versus a second-generation combined contraceptive.”

This additional information has not been supplied.

Proprietary medicinal products for which the Transparency Committee issued an Opinion in 2002:

- Products containing desogestrel/ethinylestradiol and their generics:
- CYCLEANE 20, CYCLEANE 30, MERCILON, VARNOLINE, VARNOLINE CONTINU, MIRLETTE 30 µg/150 µg, MIRLETTE 20 µg/150 µg
- Products containing gestodene/ethinylestradiol and their generics:
- HARMONET, MINESSE, MINULET, TRIMINULET, MELIANE, MELODIA, MONEVA, PHAEVA
- Product containing norgestimate/ethinylestradiol:

- CILEST

Proprietary medicinal product for which the Transparency Committee issued an Opinion in 2003:
- Product containing norgestimate/ethinylestradiol: EFFIPREV.

II.2 Re-assessment of third-generation oral contraceptives in October 2007

Following a request by the Minister of Health and Solidarity, the Transparency Committee re-assessed third-generation oral contraceptives on 10 October 2007 on the basis of current scientific knowledge with a view to possible inclusion on the list of products reimbursed by National Health Insurance.

The Committee issued an Opinion covering all third-generation oral contraceptives as part of the decision-making process on possible reimbursement.

The principal points of the analysis were:
- Since the re-assessment in 2002, there have been no new efficacy data.
- The new tolerance data show that:
  - compared with second-generation contraceptives, use of third-generation contraceptives is associated with a higher risk of venous thromboembolism. No difference between third-generation progestogens is observed; the risk of venous thromboembolism is increased regardless of the third-generation progestogen;[3]
  - in terms of arterial tolerance, the RATIO study found no difference in the risk of stroke between second- and third-generation oral contraceptives. However, a meta-analysis that assessed long-term cardiovascular safety suggested that third-generation oral contraceptives may be associated with an increased risk of stroke.
    There are no data that allow a distinction to be made between the different progestogens contained in third-generation contraceptives.
    There is no scientific argument with a sufficient level of evidence to demonstrate that third-generation oral contraceptives have a better safety profile in terms of ischaemic stroke or myocardial infarction than second-generation oral contraceptives.

These TC conclusions have, however, been amended:
"The studies included in the meta-analyses and the RATIO study are observational. The results should therefore be interpreted with caution given the potential bias associated with this type of study (selection bias, indication bias, confounding bias, assessment bias and/or measurement bias and memory bias). The level of evidence of the results is therefore low and the only conclusions possible are exploratory in nature."

The Committee concluded there was a substantial AB, but no IAB compared with second-generation oral contraceptives. It classified them as a second-line option after second-generation oral contraceptives and recommended the performance of a large-scale prospective, comparative study that allows a meaningful comparison between oral contraceptives.
"Given the increase in the risk of venous thromboembolism and ischaemic stroke associated with third-generation oral contraceptives and the lack of any prospective comparative study that is able to evaluate the benefit of third-generation oral contraceptives versus

[3] Norgestimate is a third-generation progestogen that has been little assessed. The odds ratio (norgestimate versus levonorgestrel) for the occurrence of venous thromboembolism was shown in one study to be 1.1 (95% CI [0.8; 1.6]). Jick S. et al. Risk of non fatal venous thromboembolism with oral contraceptives containing norgestimate or desogestrel compared with oral contraceptives containing levonorgestrel. Contraception 2006; 73: 566-570.

second-generation oral contraceptives, the Transparency Committee considers that third-generation oral contraceptives offer no improvement in actual benefit (IAB V) over second-generation oral contraceptives."

The proprietary medicinal products covered by this re-assessment were as follows:
- Products containing desogestrel/ethinylestradiol and their generics:
- CYCLEANE 20, CYCLEANE 30, MERCILON, VARNOLINE, VARNOLINE CONTINU, MIRLETTE 30 µg/150 µg, MIRLETTE 20 µg/150 µg
- Products containing gestodene/ethinylestradiol and their generics:
- HARMONET, MINESSE, MINULET, TRIMINULET, MELIANE, MELODIA, MONEVA, PHAEVA
- Products containing norgestimate/ethinylestradiol:
- CILEST, TRICILEST, EFFIPREV, TRIAFEMI.

II.3 Applications for inclusion on the list between 2007 and 2012

Since 2007, applications submitted by pharmaceutical companies for products to be included in the list of medicines reimbursed by National Health Insurance have resulted in the Committee recommending inclusion for 38 third-generation oral contraceptives. These 38 proprietary medicinal products were either originator medicines or were generics of originator medicines that had not been included on the list of reimbursable medicines. The Committee considered that the AB of these proprietary medicinal products was substantial, but that there was no IAB (V) compared with second-generation oral contraceptives or compared with the originator medicines. The Committee continued to classify the use of third-generation oral contraceptives as second-line options after second-generation oral contraceptives.
The list of proprietary medicinal products which received a favourable opinion is shown in Table 1.

In summary, since 2002 the Transparency Committee has considered that third-generation oral contraceptives have a substantial AB, but no IAB and since 2007 has taken the view that, because of the increased risk of venous thromboembolism, they should be prescribed only as a second-line option after first- and second-generation oral contraceptives.

Table 1: TC conclusions on third-generation contraceptives

PROPRIETARY MEDICINAL PRODUCTS	Opinion		
	Date	AB	IAB
Desogestrel/ethinylestradiol			
CYCLEANE 20 micrograms CYCLEANE 30 micrograms MSD France	10/07/2002	Substantial	V
MERCILON MSD France	10/07/2002	Substantial	V
VARNOLINE VARNOLINE CONTINU MSD France	10/07/2002 27/05/2009 10/07/2002 27/05/2009	Substantial Substantial – second line Substantial Substantial – second line	V V V V
MIRLETTE 30 µg / 150 µg MIRLETTE 20 µg / 150 µg (MA rescinded) Distrireti	10/07/2002 10/07/2002	Substantial	V
DESOBEL 150 µg / 20 µg DESOBEL 150 µg / 30 µg Effik	16/12/2009	Substantial – second line	V
DESOGESTREL ETHINYLESTRADIOL BIOGARAN 150 µg / 30 µg Biogaran	16/12/2009	Substantial – second line	V
DESOGESTREL ETHINYLESTRADIOL BIOGARAN 150 µg / 20 µg Biogaran	13/01/2010	Substantial – second line	V
DESOGESTREL ETHINYLESTRADIOL ELKA 150 µg / 20 µg DESOGESTREL ETHINYLESTRADIOL ELKA 150 µg / 30 µg DESOGESTREL ETHINYLESTRADIOL QUILL 150 µg / 20 µg DESOGESTREL ETHINYLESTRADIOL QUILL 150 µg / 30 µg Effik SA	20/10/2010 20/10/2010 20/10/2010 20/10/2010	Substantial – second line Substantial – second line Substantial – second line Substantial – second line	V V V V
Gestodene/ethinylestradiol			
HARMONET MINULET TRI MINULET Pfizer	10/07/2002 03/11/2010 10/07/2002 03/11/2010 10/07/2002 03/11/2010	Substantial Substantial – second line Substantial Substantial – second line Substantial Substantial – second line	V V V V V V
MELIANE MONEVA PHAEVA Bayer Santé	10/07/2002 31/03/2010 10/07/2002 31/03/2010 10/07/2002 31/03/2010	Substantial Substantial – second line Substantial Substantial – second line Substantial Substantial – second line	V V V V V V
MINESSE Pfizer Holding France	10/07/2002	Substantial	V
MELODIA Bayer Santé	10/07/2002	Substantial	V

Table 1 (continued)

PROPRIETARY MEDICINAL PRODUCTS	Opinion		
	Date	AB	IAB
GESTODENE ETHINYLESTRADIOL BIOGARAN 75 µg / 20 µg GESTODENE ETHINYLESTRADIOL BIOGARAN 75 µg / 30 µg Biogaran	07/04/2010 07/04/2010	Substantial – second line Substantial – second line	V V
EFEZIAL 75 µg / 20 µg EFEZIAL 75 µg / 30 µg Mylan	08/09/2010	Substantial – second line	V
CARLIN 75 µg / 20 µg CARLIN 75 µg / 30 µg Effik SA	20/10/2010	Substantial – second line	V
PERLEANE Biogaran	03/11/2010	Substantial – second line	V
GESTODENE ETHINYLESTRADIOL TEVA 75 µg / 20 µg GESTODENE ETHINYLESTRADIOL TEVA 75 µg / 30 µg Teva Santé	05/01/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL RATIOPHARM 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL RATIOPHARM 75 µg / 30 µg Ratiopharm	19/01/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL ARROW 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL ARROW 75 µg / 30 µg Arrow Generiques	20/07/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL RANBAXY 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL RANBAXY 75 µg / 30 µg Ranbaxy Pharmacie Generiques	20/07/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL WINTHROP 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL WINTHROP 75 µg / 30 µg Sanofi-Aventis France	20/07/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL SANDOZ 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL SANDOZ 75 µg / 30 µg Sandoz	05/10/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL ACTAVIS 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL ACTAVIS 75 µg / 30 µg Actavis France	05/10/2011	Substantial – second line	V
GESTODENE/ETHINYLESTRADIOL EG 75 µg / 20 µg GESTODENE/ETHINYLESTRADIOL EG 75 µg / 30 µg EG Labo – Laboratoires EuroGenerics	02/11/2011	Substantial – second line	V

Table 1 (continued)

PROPRIETARY MEDICINAL PRODUCTS	**Opinion**		
	Date	AB	IAB
Products containing norgestimate/ethinylestradiol			
CILEST Janssen Cilag	10/07/2002	Substantial	
EFFIPREV Effik	19/02/2003	Substantial	V
TRIAFEMI Effik	Not applicable		
TRICILEST Janssen Cilag	Not applicable		

Table 2: Products undergoing listing that are covered by this assessment

PROPRIETARY MEDICINAL PRODUCTS
Desogestrel/ethinylestradiol
DESOPHARM 150 µg / 20 µg DESOPHARM 150 µg / 30 µg
Gestodene/ethinylestradiol
CARLIN 60 µg / 15 µg
OPTINESSE 60 µg / 15 µg
GESTODENE/ETHINYLESTRADIOL ARROW 60 µg / 15 µg
GESPHARM 75 µg / 20 µg GESPHARM 75 µg / 30 µg

III. General description

III.1 ATC classification (2011)

- Desogestrel/ethinylestradiol

G: Genito-urinary system and sex hormones
G03: Sex hormones and modulators of the genital system
G03A: Hormonal contraceptives for systemic use
G03AA: Progestogens and estrogens, fixed combinations
G03AA09: desogestrel and ethinylestradiol

- Gestodene/ethinylestradiol

G: Genito-urinary system and sex hormones
G03: Sex hormones and modulators of the genital system
G03A: Hormonal contraceptives for systemic use
G03AA: Progestogens and estrogens, fixed combinations
G03AA10: gestodene and ethinylestradiol

- Norgestimate/ethinylestradiol

G: Genito-urinary system and sex hormones
G03: Sex hormones and modulators of the genital system
G03A: Hormonal contraceptives for systemic use
G03AA: Progestogens and estrogens, fixed combinations
G03AA11: norgestimate and ethinylestradiol

III.2 Medicines in the same therapeutic category

Strictly comparator medicines

Oral oestrogen-progestogen combination contraceptives on the market:

INN	Oestrogen dosage	Proprietary medicinal product
First-generation oestrogen-progestogen combination contraceptives (reimbursed by National Health Insurance)[4]		
Norethisterone/ethinylestradiol	Triphasic (progestogen): 35 µg	TRIELLA
Second-generation oestrogen-progestogen combination contraceptives (reimbursed by National Health Insurance)[4]		
Levonorgestrel/ethinylestradiol and their generics	Monophasic: 20 µg	LEELOO, LOVAVULO
	Monophasic: 30 µg	MINIDRIL, LUDEAL, ZIKIALE
	Biphasic: 30 and 40 µg	ADEPAL, PACILIA
	Triphasic: 30, 40 and 30 µg	TRINORDIOL, DAILY, AMARANCE, EVANECIA
Norgestrel/ethinylestradiol	Monophasic: 50 µg	STEDIRIL
Other oestrogen-progestogen combination contraceptives (not reimbursed by National Health Insurance)		
Chlormadinone acetate/ethinylestradiol	30 µg	BELARA
Drospirenone/ethinylestradiol	30 µg	JASMINE, CONVULINE, DROSPIBEL, Ethinylestradiol/drospirenone BIOGARAN
	20 µg	JASMINELLE, JASMINELLECONTINU, YAZ, BELANETTE, DROSPIBEL, RIMENDIA, Ethinylestradiol/drospirenone BIOGARAN, Ethinylestradiol/drospirenone BIOGARANCONTINU
Dienogest/estradiol valerate	3 mg/2 mg/1 mg Biphasic (progestogen)	QLAIRA
Nomegestrol acetate/estradiol	1.5 mg	ZOELY

Not-strictly-comparator medicines

- Other oestrogen-progestogen combination contraceptives:
  - EVRA, transdermal patch (norelgestromin/ethinylestradiol) (not reimbursed by National Health Insurance)
  - NUVARING, vaginal diffusion system (etonogestrel/ethinylestradiol) (not reimbursed by National Health Insurance)
- Progestogen-only contraceptives

Medicines with a similar therapeutic aim

Intrauterine devices, spermicides.

[4] As of 05/09/2012

LITERATURE SEARCHES

I. Data identified in the literature

Method

Searches covered the subjects and study types defined below (see search strategy) and were limited to publications written in English and French.

The search period was from January 2008 to March 2012.

The following sources were interrogated:
- for the international literature: the Medline database;
- the Cochrane Library;
- internet sites publishing guidelines and technological or economic assessment reports;
- internet sites of relevant learned societies (French and international) relevant to the field being studied;

This search was supplemented by the bibliography produced by the experts and by the references cited in the analysed documents.

Search strategy and results for the Medline database:

Study type/subject Terms used	Period	Number of references
– Recommendations	01/2008 – 03/201	**10**
Step 1: ("Gestodene" [Supplementary Concept] OR "ethinyl estradiol-desogestrel combination" [Supplementary Concept] OR "Desogestrel" [Mesh] OR "norgestimate, ethinyl estradiol drug combination" [Supplementary Concept] OR ((3rd generation [Title/Abstract] OR Third generation [Title/Abstract] OR "Ethinyl Estradiol" [Mesh:NoExp]) AND (("Contraceptives, Oral" [Mesh:noexp] OR "Contraceptives, Oral, Combined" [Mesh] OR "Contraceptives, Oral, Hormonal" [Mesh] OR Contraceptive* [Title]))) AND Step 2: ("Practice Guideline" [Publication Type] OR "Practice Guidelines as topic" [MeSH] OR "Guideline" [Publication Type] OR "Guidelines as topic" [MeSH] OR "Health Planning Guidelines" [MeSH] OR "Consensus Development Conferences as topic" [MeSH] OR "Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus Development Conferences, NIH as topic" [MeSH])		
– Meta-analyses and systematic reviews Step 1 AND Step 3: ("Meta-Analysis" [Publication Type] OR "Review Literature as topic" [MeSH] OR "systematic review" [ti] OR "Meta-Analysis as topic" [MeSH] OR "meta analysis" [ti])	01/2008 03/2012	**11**
– Controlled studies Step 1 AND Step 4: ("Controlled Clinical Trial" [Publication Type] OR "Controlled Clinical Trials as topic" [MeSH] OR "Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as topic" [MeSH] OR "Single-Blind Method" [MeSH] OR "Double-Blind Method" [MeSH] OR "Random Allocation" [MeSH] OR "Comparative Study" [Publication Type])	01/2008 03/2012	**168**
– Cohort studies Step 1 AND Step 5: ("Cohort Studies" [MeSH] OR "Longitudinal Studies" [MeSH] OR "Follow-Up Studies" [MeSH] OR "Prospective Studies" [MeSH])	01/2008 03/2012	**116**
– Case-control studies Step 1 AND Step 6: "Case-Control Studies" [Mesh:NoExp]	01/2008 03/2012	**23**

II. Dossiers submitted by pharmaceutical companies

The pharmaceutical companies responsible for the manufacture of the proprietary medicinal products listed in Table 1, with the exception of the products MIRLETTE 30 µg/150 µg and MIRLETTE 20 µg/150 µg, for which Marketing Authorisation has been withdrawn, were asked by HAS to supply recent evidence in support of the re-assessment of their actual benefit.

III. Data supplied by the National Medicines and Health Products Safety Agency (ANSM, formerly AFSSAPS)

On 16 April 2012, AFSSAPS set up a study group tasked with gathering the opinions of prescribers on the role of third- and fourth-generation oral combined contraceptives compared with second-generation oral combined contraceptives and reporting back to the HAS on the group's discussions and conclusions.

The principal conclusions were as follows:

1. The participants mainly prescribed second-generation oral contraceptives as the first-line option.
2. The participants were aware of the information on the risk of venous thromboembolism.
3. The clinical safety of second-generation oral contraceptives is good; third- and fourth-generation oral contraceptives have not been shown to be of greater benefit than second-generation oral contraceptives.
4. The effect on acne is similar for all generations of oral contraceptives.
5. The initial interview is important for getting an overall picture of risk factors, notably the identification of familial history of venous thromboembolism (preferably with the aid of a standard questionnaire or checklist for venous thromboembolism risk factors so as to give the interview a standardized structure).
6. To strive to educate prescribers and patients about the risk of venous thromboembolism (a campaign to heighten awareness of this by patients could be planned), while reiterating that the absolute risk is very low.
7. To strive to educate prescribers and patients about the typical signs of thrombosis.
8. To promote the circulation to prescribers of a recommendation that second-generation oral contraceptives should be the preferred first-line option wherever possible (in conjunction with HAS).
9. To take action to tackle under-reporting of adverse effects by increasing awareness among health professionals.

CLINICAL DATA: ANALYSIS OF DATA PUBLISHED SINCE THE LAST RE-ASSESSMENT OF THIRD-GENERATION ORAL CONTRACEPTIVES (OCTOBER 2007)

I. Efficacy

The efficacy of methods of contraception is based on calculation of the Pearl Index (number of pregnancies per 100 woman-years).
For all third-generation oral contraceptives, this index is between 0 and 0.77 (see SPCs of individual proprietary products).
No new data on the efficacy of third-generation oral contraceptives has been submitted by the pharmaceutical companies or identified in the literature.

II. Safety

II.1 Risk of myocardial infarction

A prospective Swedish cohort study[5] examined the relationship between occurrence of myocardial infarction and the use of oral contraceptives.
This study was carried out in women aged between 30 and 49 years selected at random from a population register. Recruitment took place in 1991-1992. Information on past and present use of oral contraception was collected with the aid of a questionnaire at the time of inclusion.
Follow-up as regards the occurrence of fatal or nonfatal myocardial infarction was carried out on the basis of national registers of deaths and hospitalizations. No information was collected on the use of oral contraceptives after inclusion. The final analysis was carried out on a total of 48,321 women. The mean duration of follow-up was 11 years.
For each comparison, a reference group made up of women who had never used oral contraception was used.
There was no evidence of an increase in the risk of myocardial infarction (adjusted for age and for cardiovascular risk factors) in women who had used oral contraceptives, whether or not they had stopped them at the time of inclusion. RR = 1; 95% CI: [0.7-1.4].
No evidence was found of any increase in risk according to the type of contraception (generation of progestogen and oestrogen dose).

An analysis of a Danish cohort[6] examined the risk of a first ischaemic stroke and first myocardial infarction in women using hormonal contraception. Transient ischaemic attacks were not included in the study. This cohort was followed for 15 years, from January 1995 to December 2009. It was made up of Danish women aged from 15 to 49 years who were not pregnant and had no history of cancer, hysterectomy, oophorectomy or sterilisation. The data were collected from four sources: Danish statistics (personal identification number of each individual citizen), the national patient register (discharge diagnosis for each hospital stay), national register of causes of death and national register of medicinal products (data on prescriptions of oral contraceptives). The analysis was stratified according to dose of ethinylestradiol (50 µg, 30 to 40 µg, or 20 µg), progestogen type and duration of use. The reference group was made up of women who had never used hormonal contraception or who had stopped. The assessment of risks was adjusted for age, calendar year, level of education and cardiovascular risk factors. Tobacco consumption was likewise taken into account. There was no significant difference in risk between women who had never used

[5] Margolis K, Adami H-O, Luo J, Ye W, Weiderpass E. A prospective study of oral contraceptive use and risk of myocardial infarction among Swedish women. Fertil Steril 2007; 88: 310-316.
[6] Lidegaard O, Lokkegaard E et al. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012; 336: 2257-66.

hormonal contraception and those who had stopped. A total of 1051 women who had had a stroke and 497 who had had a myocardial infarction were identified for 4.9 million woman-years of use of hormonal contraceptives.
The relative risk of ischaemic stroke and myocardial infarction did not differ significantly according to progestogen type for oral contraceptives containing 30 to 40 µg of estradiol.
There was no significant increase in the risk of ischaemic stroke and myocardial infarction in women using oral contraception for oral contraceptives containing 20, 30 to 40 and 50 µg of ethinylestradiol. There was a significant trend towards an increased risk of myocardial infarction with increasing dose of ethinylestradiol. The trend was not significant for ischaemic stroke. The results are shown in Table 2.

Table 2: Risk of ischaemic stroke and myocardial infarction in women using oral contraception according to dose of ethinylestradiol*

Dose of ethinylestradiol	20 µg	30 to 40 µg	50 µg	p of trend
Ischaemic stroke: RR [95% CI]	1.60 [1.37; 1.86]	1.75 [1.61; 1.92]	1.97 [1.45; 2.66]	p = 0.24
MI: RR [95% CI]	1.40 [1.07; 1.81]	1.88 [1.66; 2.13]	3.73 [2.78; 5.00]	p < 0.001

Stroke = cerebrovascular accident; MI: myocardial infarction; RR: relative risk; CI: confidence interval; *: analysis adjusted for progestogen type, age and calendar year

II. 2 Risk of venous thromboembolism

A case-control study carried out in six hospitals in the Netherlands[7] examined thromboembolism risk factors. The study, which was conducted from March 1999 to September 2004, included all patients under 70 years of age who had had a first episode of Doppler-confirmed deep-vein thrombosis in the arms or legs or of pulmonary embolism confirmed by scintigraphy, spiral computed tomography or angiography. For the analysis examining the risk associated with oral oestrogen-progestogen combination contraceptives as a function of oestrogen dose and progestogen type used, only women aged between 18 and 50 years were included. The controls were either the patients' partners or were selected on the basis of telephone numbers chosen at random in the same region as the cases included. A total of 1524 patients and 1760 controls were included. The odds ratios were adjusted for age and period of inclusion. For women who were not using oral contraception, the odds ratio was 3.6 [2.9-4.6] for contraceptives containing levonorgestrel, 3.9 [1.4; 10.6], for those containing norethisterone, 5.6 [3.7-8.4], for those containing gestodene, 7.3 [5.3-10.0] for those containing desogestrel, and 5.9 [1.7-21] for those containing norgestimate. For norgestimate, it should be noted that these data are based on a small number of cases: nine cases, which included four pulmonary embolisms in contraceptive users and four cases of deep-vein thrombosis in the controls.
Oral contraceptives containing gestodene (OR = 1.6 [1-2.4]) and desogestrel (OR = 2.0 [1.4-2.8]) were associated with an increased risk of thromboembolism compared with those containing levonorgestrel. The result was not given for norgestimate.
Investigation of the effect of the oestrogen dose was limited to monophasic products containing levonorgestrel, gestodene or desogestrel. Compared with contraceptives containing an oestrogen dose of 30 µg, the risk of thrombosis was higher (OR = 1.9 [1.1-3.4]) for those containing 50 µg and not significantly different (OR = 0.8 [0.5-1.2]) for those containing 20 µg.
The dependence of thromboembolic risk on duration of contraception was examined for levonorgestrel, gestodene and desogestrel in a pooled analysis. The risk was higher in the

[7] Van Hycklama Vlieg A, Helmerhorst FM, et al. The venous thrombotic risk of oral contraceptives, effect of estrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009; 339: b 2921.

first three months of contraception: OR 12.6 [7.1-22.3], then OR = 8.3 [4.7-14.5] between 3 and 6 months, OR = 7.5 [4.7-12.2] between 6 and 12 months and OR = 5 [3.4-7.4] between 12 and 24 months; after that the risk remained much the same for periods up to or more than 60 months.

A Danish cohort study[8] carried out on the basis of data from four national registers (population, level of education, medical prescriptions, hospitalisations with their diagnosis) assessed the risk of thromboembolism in women using hormonal contraception. The study was conducted from January 1995 to December 2005. The study population comprised Danish women aged between 15 and 49 years who were not pregnant and had no history of cancer or cardiovascular disease. The events covered were:first occurrence during the study of a deep-vein thrombosis, thrombosis of the hepatic portal vein, vena cava, or renal vein, deep-vein thrombosis of unstated localisation, or pulmonary embolism. The contraception data that was recorded comprised the period of use (ongoing, past or never), method used (oral combined contraceptives, oral progestogen only, or progestogen-releasing IUD), oestrogen dose (50 µg, 30-40 µg or 20 µg), progestogen type (norethisterone, levonorgestrel, norgestimate, desogestrel, gestodene, drospirenone or cyproterone), duration of use of oral combined contraceptives for current users (< 1 year, 1-4 years or > 4 years). The analysis covered 3.4 million woman-years for current users. A total of 4213 first thrombotic episodes were documented, of which 2045 occurred in women using oral contraception. The results were adjusted for age, calendar year, level of education and duration of use.
The incidence of thromboembolic events was 6.29/10,000 woman-years in users of oral contraception and 3.01/10,000 woman-years in non-users.
In users of oral oestrogen-progestogen combined contraceptives, the risk of thromboembolism decreased with the dose of oestrogen for a given progestogen: non-significant decrease in risk when going from 50 to 30-40 µg for levonorgestrel (17%) and for norethisterone (32%); significant decrease in risk when going from 30-40 to 20 µg for desogestrel and gestodene (18%). This risk also decreased with duration of use (all oral oestrogen-progestogen combined contraceptives taken together): incidence ratio = 4.17 [3.73; 4.66] during the first year to 2.76 [2.53; 3.02] after more than four years of use.
Compared with oral oestrogen-progestogen combined contraceptives containing levonorgestrel and for the same oestrogen dose, the incidence ratio for thromboembolic events was significantly higher for oral contraceptives containing desogestrel (1.82 [1.49-2.22]) and gestodene (1.86 [1.59-2.18]); the ratio was 0.98 [0.71-1.37] for norethisterone and 1.19 [0.96-1.47] for norgestimate.

A case-control study[9] carried out in Austria compared the risk of thromboembolism in women using oral contraceptives containing gestodene with the risk in users of second-generation oral contraceptives. Women eligible for the study had to be aged between 15 and 49 years and to have had a firm (confirmed by at least one imaging examination) or probable (established by a different test and followed by anticoagulant therapy for a period of weeks or months) diagnosis of deep vein thrombosis or pulmonary embolism between January 2002 and February 2006. The 427 confirmed or probable cases were identified on the basis of questionnaires sent to their gynaecologists. Neither the number of doctors contacted nor the percentage of responses were stated. A total of 1920 controls were selected. They had to reside in the same region and have the same year of birth as the cases. Their method of recruitment was not stated.
The odds ratio for all thromboembolisms (adjusted for age, BMI, parity and previous use of hormonal contraception) versus non-users of oral contraception was 3.39 [2.36-4.87] for oral

8 Lidegaard O, Lokkegaard E et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ, 2009; 339: b2890.
9 Heinemann LA et al. Use of oral contraceptives containing gestodene and risk of venous thromboembolism: outlook 10 years after the third-generation “pill scare”. Contraception 2010; 81: 401-407.

contraceptives containing gestodene and 3.14 [2.21-4.47] for second-generation oral contraceptives.
The adjusted odds ratio versus non-users of oral contraception for idiopathic thromboembolisms was 8.1 [5.02-13.07] for oral contraceptives containing gestodene and 6.87 [4.32-10.94] for second-generation oral contraceptives.
The adjusted odds ratio for oral contraceptives containing gestodene versus second-generation oral contraceptives for all thromboembolisms and for idiopathic thromboembolisms was close to 1 and not statistically significant.
The authors concluded there was no difference in the risk of thromboembolism between second-generation oral contraceptives and those containing gestodene.
This study was financed by a pharmaceutical company marketing oral contraceptives, including contraceptives containing gestodene.

A study[10] carried out in Denmark on the same cohort as a previous publication[6] examined the risk of a first venous thromboembolism in women using oral oestrogen-progestogen combined contraceptives as a function of progestogen type and oestrogen dose. This cohort comprised all Danish women aged from 15 to 49 years between 1995 and 2009. The data were collected from four sources: Danish statistics (personal identification number of each individual citizen), the national patient register (discharge diagnosis for each hospital stay), national register of causes of death and national register of medicinal products (data on prescriptions of oral contraceptives). Women who had had cancer or venous or arterial thromboembolism, bilateral oophorectomy, hysterectomy or sterilisation prior to the study and women with known coagulation disorders (protein C, protein S or antithrombin III deficiency, factor V Leiden, prothrombin 20210 mutation) were excluded from the analysis; the data for women who had had cancer, bilateral oophorectomy, hysterectomy or sterilisation or who had undergone treatment to stimulate ovulation during the study were marked at the time of the diagnosis or intervention; data were also marked during pregnancy and for the first three months after childbirth. The data collected on oral contraceptives concerned the progestogen type, oestrogen dose and duration of use. Cases were considered to be confirmed if they were followed by a course of anticoagulation therapy lasting at least four weeks.
The medical records of 200 cases selected at random were assessed for clinical signs with confirmation by ultrasonography, phlebography, imaging or scintigraphy and by a course of anticoagulation therapy lasting at least four weeks after diagnosis. The assessment was carried out blinded for use of oral contraceptives.
The analysis was stratified for age, duration of use, level of education and calendar year.
A total of 1296 women were included in the analysis, for a duration of follow-up of 8,010,290 woman-years; 4307 first episodes of thromboembolism were recorded, of which 2847 were confirmed. Compared with non-users, the relative risk of a confirmed first thromboembolism for users of oral contraceptives containing 30-40 µg of ethinylestradiol was 2.2 [1.1; 4.5] in combination with norethisterone, 2.9 [2.2; 3.8] with levonorgestrel, 6.6 [5.6; 7.8] with desogestrel, 6.2 [5.6; 7.0] with gestodene and 3.5 [2.9; 4.3] with norgestimate.
Compared with users of oral contraceptives containing 30-40 µg of ethinylestradiol in combination with levonorgestrel and adjusted for the duration of use, the risk of a confirmed thromboembolism in users of contraceptives containing 30-40 µg of ethinylestradiol was 2.2 [1.7; 3] in combination with desogestrel and 2.1 [1.6; 2.8] in combination with gestodene: no significant increase in risk was observed with contraceptives containing norethisterone (0.8 [0.4; 1.6]) or norgestimate (1.2 [0.9; 1.6]).
The risk relative to non-users decreased with duration of use for levonorgestrel (RR = 4.1 [2.7; 6.2] for less than 3 months of use to 1.9 [1.5; 2.4] for more than 4 years of use) and for norgestimate (RR = 3.8 [2.6; 5.6] for less than 3 months of use to 1.8 [1.3; 2.6] for more than 4 years of use). However, it was not stated whether this decrease is significant.

10 Lidegaard O et al. Risk of 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.

The risk did not decrease with duration of use for desogestrel (RR = 4.6 [3.01; 7] for less than 3 months of use to 4.6 [3.6; 5.9] for more than 4 years of use) or for gestodene (RR = 4.8 [3.9; 6.1] for less than 3 years of use to 3.9 [3.4; 4.5] for more than 4 years of use).

A systematic review[11] of studies published between January 1995 and April 2010 examined the effect of combined hormonal contraceptives on the risk of venous thromboembolism irrespective of their route of administration. The publications included were observational studies: these were case-control studies and cohort studies. The analyses included the studies of van Hycklama (2009) and Lidegaard (2009).
Two analyses have compared contraceptives containing gestodene with those containing levonorgestrel. In one of these, comprising eight case-control studies, the odds ratio was 1.49 [1.13-1.96], but with significant heterogeneity between the studies. In the other, comprising five cohort studies, the relative risk was 1.33 [1.08-1.63].
Two analyses have compared contraceptives containing desogestrel with those containing levonorgestrel. In one of these, comprising ten case-control studies, the odds ratio was 1.62 [1.33-1.97], but with significant heterogeneity between the studies. In the other, comprising eight cohort studies, the relative risk was 1.93 [1.31-2.85] and there was again significant heterogeneity between the studies.
An analysis comprising four case-control studies compared contraceptives containing norgestimate with those containing levonorgestrel: the odds ratio was 1.11 [0.84; 1.46].

II.3 Clinical tolerance

The COCON[12] study compared the frequency of clinical symptoms (weight gain, nausea, mastalgia, amenorrhoea, metrorrhagia, dysmenorrhoea, hypermenorrhoea, heavy legs) as a function of type of oral contraception (oestrogen dose, progestogen type, dosing regimen).
This was a telephone survey carried out on a representative sample of 2,863 women living in France, aged between 18 and 44 years and interviewed once a year between 2000 and 2004.
The sole significant difference between second- and third-generation oral combined contraceptives was a decrease in the frequency of menstruation, reported significantly more often by users of third-generation oral contraceptives (OR 2.3; [95% CI: 1.1-5.7], p = 0.01). However, in a subgroup analysis of women using oral contraceptives containing 30 µg of oestrogen, women using an oral contraceptive containing desogestrel reported a decrease in the frequency of menstruation less often than women using an oral contraceptive containing levonorgestrel (OR 0.2; [95% CI: 0.03-0.6], p = 0.01).
This survey did not therefore demonstrate a difference in clinical tolerance between second- and third-generation contraceptives.

A systematic Cochrane review[13] compared oral contraceptives containing 20 µg of ethinylestradiol with those containing a higher dose in terms of efficacy, bleeding and discontinuation rate. The authors concluded that the data from randomised studies were insufficient to detect any difference in efficacy. A higher incidence of bleeding problems and discontinuation was observed with contraceptives containing a low oestrogen dose. However, most of the studies compared oral contraceptives containing different progestogens, which could also be the origin of the differences in bleeding patterns.

[11] Martinez F. et al. Venous and pulmonary thromboembolism and combined hormonal contraceptives. Systematic review and meta-analysis. Eur. J. Reprod. Contracept. Reprod. Health Care. 2012; 17: 7-29.
[12] Moreau C, Trussell J, Gilbert F, Bajos N, Boyer J. Oral contraceptive tolerance – does the type of pill matter?. Obstetrics and gynecology 2007; 109: 1277-1285.
[13] Gallo MF, Nanda K, et al. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD003989. DOI:10.1002/14651858. CD003989.pub3.

A systematic Cochrane review[14] examined the efficacy of oral combined contraceptives in the treatment of facial acne compared with placebo or other active treatments during randomised controlled studies. An analysis of two studies that compared a combination of levonorgestrel (100 µg) and ethinylestradiol (20 µg) with placebo found a significant improvement among women using oral contraceptives in the total number of lesions, inflammatory lesions and non-inflammatory lesions and in the percentage of women in whom lesions were almost completely or totally absent at the doctor's and user's assessments at cycle 6.
An analysis of two studies that compared a combination of norgestimate (triphasic) and ethinylestradiol (35 µg) with placebo found a significant improvement among women given the active treatment in the total number of lesions, inflammatory lesions and comedones and in the percentage of women in whom lesions were almost completely or totally absent at the doctor's assessment at cycle 6.
Three studies have compared a combination of levonorgestrel and ethinylestradiol with a combination of desogestrel and ethinylestradiol. A pooled analysis was not carried out. Two of these studies compared a levonorgestrel 100 µg / ethinylestradiol 30 µg combination with a desogestrel 150 µg / ethinylestradiol 30 µg combination; one study concluded an improvement in women using the contraceptive containing levonorgestrel compared with the product containing desogestrel, the other did not find any difference between groups. A study that compared two contraceptives containing the same two progestogens at the same doses in combination with 20 µg of ethinylestradiol concluded a more favourable result for the combination containing desogestrel than for the combination with levonorgestrel.
The authors concluded that there was an improvement in acne in women using oral contraceptives compared with placebo, without any clear difference in efficacy between the different types of oral contraceptives.

A systematic Cochrane review[15] examined a possible association between use of combined oral contraceptives and changes in body weight during randomised controlled studies. There was no pooled analysis of the studies. A comparison of levonorgestrel 100 µg / ethinylestradiol 20 µg versus placebo showed no significant change in weight after six cycles of treatment. The same was observed in a study comparing a combination of norgestrel 300 µg / ethinylestradiol 30 µg versus no treatment. There was no mention of any studies comparing third-generation oral contraceptives with placebo or with no treatment.
Three studies have compared a first-generation oral contraceptive (containing norethisterone) with a second-generation oral contraceptive (containing levonorgestrel). No significant difference between these treatments was observed.
Two studies have compared a first-generation oral contraceptive (containing norethisterone) with a third-generation oral contraceptive: one study showed a significant difference in favour of contraceptives containing desogestrel, the other showed no significant difference with the contraceptive containing norgestimate.
Six studies have compared second-generation contraceptives (containing levonorgestrel) with third-generation contraceptives. Five of these studies used oral contraceptives containing desogestrel: one concluded that there was a significant difference in favour of levonorgestrel, the other four showed no significant difference. One study that used an oral contraceptive containing gestodene found this to be significantly superior.
The authors concluded that there was no evidence for oral contraceptives having any appreciable effect on body weight.

A systematic Cochrane review[16] compared oral contraceptives containing low-dose estradiol (< 50 µg) in combination with different progestogens in terms of contraceptive efficacy,

[14] Arowojolu et al. Combined oral contraceptive pills for treatment of acne. Cochrane database of systematic reviews 2009, Issue 3. Art. No.: CD004425.
[15] Gallo MF et al. Combination contraceptives: effects on weight. Cochrane database of systematic reviews 2011, Issue 9. Art. No.: CD003987.
[16] Lawrie et al. Types of progestogens in combined oral contraception: effectiveness and side-effects. Cochrane database of systematic reviews 2011, Issue 5. Art. No.: CD004861.

continuation rate, control of the cycle and adverse effects during randomised controlled studies.
The data were insufficient to conclude any difference in terms of contraceptive efficacy.
Second-generation contraceptives were found to show significant superiority over first-generation contraceptives in terms of discontinuation rate (three studies: norethisterone versus norgestrel or levonorgestrel). This comparison concerned only monophasic oral contraceptives.
Third-generation contraceptives were found to show significant superiority over second-generation contraceptives in terms of discontinuation rate (three studies). However, this difference was no longer significant when the comparison was confined to double-blind studies (two studies). This comparison concerned only monophasic oral contraceptives.
Breakthrough bleeding was less frequent with third-generation oral contraceptives than with second-generation oral contraceptives in one double-blind study (gestodene versus levonorgestrel).
No difference between second- and third-generation contraceptives was found in the number of discontinuations not linked to cycle problems, discontinuations linked to cycle problems, adverse effects other than cycle problems taken together, and in mastalgia, headache and “other adverse effects” examined separately.
No comparison was made between contraceptives containing norgestimate and those containing levonorgestrel.
No differences in tolerance criteria were found between contraceptives containing desogestrel and levonorgestrel, between those containing gestodene and levonorgestrel, and between first- and third-generation contraceptives.
The authors concluded that the superiority of oral contraceptives containing gestodene over those containing levonorgestrel in terms of breakthrough bleeding needed confirmation.

III. Conclusion

No data were identified that revealed any difference in efficacy between third-generation and first- and second-generation contraceptives.

Risk of myocardial infarction and stroke:
A Swedish cohort study found no evidence of an increase in the risk of myocardial infarction (adjusted for age and cardiovascular risk factors) in women who were current or past users of oral contraceptives or of any difference in risk associated with the type of contraception (progestogen generation and oestrogen dose).

An analysis of a Danish cohort examined the risk of a first ischaemic stroke and first myocardial infarction in women using hormonal contraception. The reference group was made up of women who had never used hormonal contraception or who had stopped. This study concluded that there was a significant increase in the risk of ischaemic stroke and myocardial infarction in women using oral contraception, with no significant difference associated with progestogen type. There was a significant trend towards an increased risk of myocardial infarction with increasing dose of ethinylestradiol. The trend was not significant for ischaemic stroke.

Risk of venous thromboembolism:
For gestodene and desogestrel, a case-control study, two studies carried out several years apart on the same cohort, and a systematic review concluded a significant increase in the risk of thromboembolism in women using third-generation oral contraceptives containing gestodene or desogestrel compared with second-generation oral contraceptives containing levonorgestrel. In the case-control study and the two cohort studies, there was no increased risk for first-generation oral contraceptives containing norethisterone compared with second-generation products containing levonorgestrel.
For gestodene, the risk in these studies ranged from 1.3 [1.1; 1.6] to 2.1 [1.6; 2.8] relative to levonorgestrel. For desogestrel, the risk in these studies ranged from 1.8 [1.5; 2.2] to 2.2 [1.7; 3] relative to levonorgestrel. Only one case-control study found no evidence of a difference in the risk of thromboembolism between oral contraceptives containing gestodene and second-generation oral contraceptives.
For norgestimate, a case-control study concluded that there was an increase in the risk of thromboembolism versus non-users of the same order as that observed with gestodene and desogestrel. Two studies carried out four years apart on the same cohort and a systematic review did not find any significant increase in the risk of thromboembolism in women using third-generation oral contraceptives containing norgestimate compared with second-generation oral contraceptives containing levonorgestrel.
In a cohort study, the risk decreased with duration of use for levonorgestrel and for norgestimate. No decrease with duration of use was observed for desogestrel or for gestodene.

The Transparency Committee notes that the level of evidence for an increased risk with norgestimate is not as high as that of gestodene and desogestrel. However, it considers that the available data do not currently allow norgestimate to be distinguished from gestodene and desogestrel in terms of increased risk of venous thromboembolism. The Transparency Committee will therefore remain vigilant for any new scientific data on norgestimate in particular.

Thus, for women using third-generation oral contraceptives, there is no reason for any abrupt move away from such products. This change is a decision that must be taken at the end of the current prescribed course (of 3 to 6 months), by agreement with the prescriber.

Clinical tolerance

Acne:

A systematic Cochrane review examined the efficacy of oral combined contraceptives in the treatment of facial acne compared with placebo or with other active treatments during randomised controlled studies.

An analysis of two studies that compared a combination of levonorgestrel (100 µg) and ethinylestradiol (20 µg) with placebo found a significant improvement in acne in women using oral contraceptives. An analysis of two studies that compared a combination of norgestimate (triphasic) and ethinylestradiol (35 µg) with placebo found a significant improvement in acne in women using oral contraceptives.

It was not possible to carry out a pooled analysis of studies comparing second- and third-generation oral contraceptives. On the other hand, the results of these studies do not paint a uniform picture. The authors concluded that there was an improvement in acne in women using oral contraceptives compared with placebo, without any clear difference in efficacy between the different types of oral contraceptives.

Weight gain:

A systematic Cochrane review examined a possible association between use of oral combined contraceptives and changes in body weight during randomised controlled studies.

It was not possible to carry out a pooled analysis of studies. The authors concluded that there was no evidence for oral contraceptives having any appreciable effect on body weight.

Control of the cycle and other clinical symptoms:

A systematic Cochrane review has compared oral contraceptives containing 20 µg of ethinylestradiol with those containing a higher dose in terms of bleeding and discontinuation rate. Although bleeding and discontinuations had been more frequent with the low-dose pill, the authors were unable to draw any conclusions, as the majority of studies had compared oral contraceptives containing different progestogens that could also have been the origin of the observed differences.

A systematic Cochrane review has compared oral contraceptives containing low-dose estradiol (< 50 µg) and different progestogens in terms of contraceptive efficacy, continuation rate, control of the cycle and adverse effects during randomised controlled studies.

For oral monophasic contraceptives, third-generation products were found to be significantly superior in terms of discontinuation rate; this difference was no longer significant when the comparison was confined to double-blind studies. Breakthrough bleeding was less frequent with third-generation oral contraceptives than with second-generation oral contraceptives in one double-blind study (gestodene versus levonorgestrel). No difference between second- and third-generation contraceptives was found in the number of discontinuations not linked to cycle problems, discontinuations linked to cycle problems, other adverse effects taken together, and in mastalgia, headache and others examined separately.

The authors concluded that the superiority of oral contraceptives containing gestodene over those containing levonorgestrel in terms of breakthrough bleeding needed confirmation.

A telephone survey has compared the frequency of clinical symptoms (weight gain, nausea, mastalgia, amenorrhoea, metrorrhagia, dysmenorrhoea, hypermenorrhoea, heavy legs) as a function of type of oral contraception (oestrogen dose, progestogen type, dose regimen).

This survey did not demonstrate a difference in clinical tolerance between second- and third-generation contraceptives.

Third-generation oral contraceptives containing 15 µg of ethinylestradiol

In the absence of adequate tolerance data, no distinction can be made between third-generation combined contraceptives containing less than 20 µg of ethinylestradiol and other third-generation combined contraceptives.

Place of third-generation oral contraceptives in the contraceptive strategy

Since 2007, the Transparency Committee has recommended that third-generation oral contraceptives be prescribed only as a second-line option. However, the notion of what constitutes second-line could be understood differently by different prescribers:

- in established cases of intolerance after trying a first- or second-generation contraceptive,
- in established cases of intolerance after trying more than one first- or second-generation oral contraceptive in succession,

this corresponds to a second-line situation

- on institution of treatment after the prescriber had ruled out first- or second-generation oral contraceptives on the basis of the woman's medical history or particular circumstances,

this interpretation is equivalent to a first-line situation.

The new data available no longer allow third-generation oral contraceptives to be positioned as a second-line option.

USAGE DATA

Study of the prescription of oral contraceptives based on IMS data*

	2009	2010	2011
First generation			
Cumulative number of prescriptions, in 000s	165	143	84
GENERAL PRACTITIONERS, %	65.2	70.5	73.2
GYNAECOLOGISTS, %	34.1	28.8	26.8
DERMATOLOGISTS, %	0.7	0.7	0.0
Second generation			
Cumulative number of prescriptions, in 000s	3542	3306	3219
GENERAL PRACTITIONERS, %	66.0	68.0	68.0
GYNAECOLOGISTS, %	33.8	31.7	31.2
DERMATOLOGISTS, %	0.4	0.3	0.6
ENDOCRINOLOGISTS, %	0.1	0.1	0.0
Third generation			
Cumulative number of prescriptions, in 000s	1762	2185	2058
GYNAECOLOGISTS, %	62.3	57.3	54.2
GENERAL PRACTITIONERS, %	37.2	42.3	44.7
DERMATOLOGISTS, %	0.2	0.2	0.9
ENDOCRINOLOGISTS, %	0.2	0.1	0.1
NEUROPSYCHIATRISTS, %	0.0	0.0	0.1
PAEDIATRICIANS, %	0.1	0.0	0.0

*Source: AFSSAPS, April 2012

Sales figures: Course of market share of COC (Source AFSSAPS. Figures for the whole of France, including sales to hospitals)

	2007	2008	2009	2010
First generation	3.6%	3.5%	3.0%	1.5%
Second generation	54.5%	53.8%	52.7%	50.0%
Third generation	32.3%	30.3%	29.3%	32.0%
Other oral oestrogen-progestogen combined contraceptives	9.6%	12.5%	15%	16.5%

TRANSPARENCY COMMITTEE CONCLUSIONS

I Re-assessment of actual benefit (AB)

Access to contraception that is safe, effective and suitable for all women who choose to use it is a public health priority.

Such proprietary medicinal products are used to prevent unwanted pregnancies.

Taking into account the efficacy data (unchanged since previous Committee assessments), but with tolerance data having confirmed and quantified an increased risk of venous thromboembolic events compared with second-generation (containing norgestrel or levonorgestrel in combination with ethinylestradiol) and first-generation (containing norethisterone in combination with ethinylestradiol) oral contraceptives, the efficacy/adverse effects ratio must be considered to be low.

> Public health benefit
> Ensuring access to suitable contraception and reducing the frequency of voluntary terminations of pregnancy are public health objectives defined by the National Technical Group for the Definition of Public-Health Objectives (GTNDO).
> There is therefore a public health need, but the response to this need does not necessarily mean reimbursement of new oral contraceptives.
> On the basis of the available data, the impact in terms of any increase in contraceptive coverage brought about by reimbursing the costs of third-generation oral contraceptives could be offset by the increase in venous thromboembolic events in healthy women taking third-generation oral contraceptives compared with first- and second-generation oral contraceptives.
> Third-generation oral contraceptives are not therefore expected to benefit public health.

There are numerous alternatives to these contraceptives.

Following on from previous Transparency Committee Opinions, the new data that are available no longer allow third-generation oral contraceptives to be positioned as a second-line option.

In 2012 the Transparency Committee considers that, taking into account both the increased risk of venous thromboembolic events and the lack of demonstrated benefit in terms of clinical safety in women exposed to third-generation oral contraceptives compared with second- or first-generation oral contraceptives, the actual benefit of these proprietary medicinal products must be regarded as **insufficient** for reimbursement by National Health Insurance.