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TRANSPARENCY COMMITTEE

Opinion
19 February 2014

ANTIGONE 75 µg, coated tablet

B/28 (CIP: 34009 224 741 4 4)

B/56 (CIP: 34009 224 742 0 5)

B/84 (CIP: 34009 224 743 7 3)

Applicant: BESINS INTERNATIONAL

INN	desogestrel
ATC Code (2013):	G03AC09 (hormonal contraceptives-progestogens)
Reason for the request	Inclusion
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123 2)
Indication concerned	"Contraception."

Actual Benefit	Substantial
Improvement in Actual Benefit	ANTIGONE does not provide an improvement in actual benefit (IAB V, non-existent) in the management of contraception.
Therapeutic use	ANTIGONE is a first-line medicinal product, especially postpartum, when breastfeeding¹ and in certain situations in women at cardiovascular risk (see HAS memo).²

¹ HAS - Fiche memo – contraception chez la femme en post-partum - juillet 2013 [memo sheet-contraception in postpartum women - July 2013]

² HAS - memo sheet-contraception in women at cardiovascular risk July 2013

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	27 September 2012 (decentralised procedure)
Prescribing and dispensing conditions	List I
ATC Classification	2012 G Genito urinary system and sex hormones G03 Sex hormones and modulators of the genital system G03A Hormonal contraceptives for systemic use G03AC Progestogens G03AC09 desogestrel

02 BACKGROUND

This is a request for inclusion of the proprietary medicinal product ANTIGONE, which is a generic form of CERAZETTE, a proprietary medicinal product for which inclusion was requested in 2002, having obtained a substantial AB and an IAB V (Committee opinion of 8 November 2000) but which remains non-reimbursable.

03 THERAPEUTIC INDICATION

"Contraception"

04 DOSAGE

"How to take ANTIGONE 0.075 mg, film coated tablet

One tablet per day without interruption at the same time so that the interval between two tablets always is 24 hours.

The first tablet should be taken on the first day of menstrual bleeding.

Thereafter one tablet is to be taken continuously each day, without taking any notice of possible bleeding.

A new blister is started directly on the day after the previous one is finished.

How to start ANTIGONE 0.075 mg, film coated tablet

No preceding hormonal contraceptive use (in the past month):

Tablet-taking has to start on day 1 of the woman's menstrual cycle (i.e., first day of menstrual bleeding). Starting on days 2-5 is allowed, provided that a barrier method (e.g. a condom) is used for the first 7 days of taking ANTIGONE.

Following first-trimester abortion:

After first-trimester abortion, it is recommended to start the treatment immediately. In that case there is no need to use an additional barrier method of contraception.

Following delivery or second-trimester abortion:

Contraceptive treatment with ANTIGONE after delivery can be initiated before return of menstruation. If more than 21 days have elapsed since delivery, pregnancy should be ruled out before taking ANTIGONE and an additional barrier method of contraception should be used for the first week of taking contraceptive tablets.

For additional information for breastfeeding women see the section on pregnancy and lactation.

How to start ANTIGONE 0.075 mg, film coated tablet when changing from other contraceptive methods

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch).

The woman should start ANTIGONE preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC or on the day of removal of her vaginal ring or transdermal patch. In these cases, the use of an additional barrier contraceptive is not necessary.

Not all contraceptive methods may be available in all EU countries.

The woman may also start ANTIGONE at the latest on the day following the usual tablet free, patch-free, ring-free, or placebo tablet interval of her previous COC. However, during the first 7 days of tablet-taking an additional barrier method is recommended.

Changing from a progestogen-only-method (minipill, injection, implant or from a progestogen-releasing intrauterine system).

The woman may switch any day from the minipill (from an implant or a progestogen-releasing intrauterine system on the day of its removal, from an injectable when the next injection would be due).

Management of missed tablets

Contraceptive protection may be reduced if more than 36 hours have elapsed between two tablets. If the user is less than 12 hours late in taking any tablet, the missed tablet should be taken immediately and the next tablet should be taken at the usual time.

If she is more than 12 hours late, the user should take the last tablet forgotten as soon as she remembers and take the next tablet at the usual time, even if this means taking two tablets at the same time. In addition, she should use a barrier method of contraception (e.g. a condom) for the next 7 days. If tablets were missed in the first week and sexual intercourse took place in the 7 days before the tablets were missed, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets is applicable.

Treatment surveillance

Before prescription, a thorough case history should be taken and a thorough gynaecological examination is recommended to exclude pregnancy. Bleeding disturbances, such as oligomenorrhoea and amenorrhoea should be investigated before prescription.

The interval between check-ups depends on the circumstances in each individual case. If the prescribed product may influence latent or manifest disease (see the section on special warnings and precautions for use), the check-ups should be timed accordingly.

Despite the fact that ANTIGONE is taken regularly, bleeding disturbances may occur. If bleeding is very frequent or irregular, another contraceptive method should be considered. If the symptoms persist, an organic cause should be ruled out.

Management of amenorrhoea during treatment depends on whether or not the tablets have been taken in accordance with the instructions and may include a pregnancy test.

The treatment should be stopped if a pregnancy occurs.

Women should be advised that ANTIGONE does not protect against HIV (AIDS) and other sexually transmitted diseases.

Paediatric population

The safety and efficacy of desogestrel in adolescents below 18 years has not been established. No data are available."

05 THERAPEUTIC NEED

ANTIGONE is a generic of CERAZETTE, a non-reimbursable proprietary medicinal product. There is another reimbursable progestogen oral contraceptive: MICROVAL.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Progestogen contraceptives

The comparators for ANTIGONE are oral progestogens indicated in contraception.

6.1.1 Progestogen oral contraceptives

NAME (INN) Company	Same TC* Yes/No	Indication	Date of opinion	AB	IAB (Wording)	Reimbursement Yes/No
CERAZETTE (desogestrel) MSD FRANCE and other generics	Yes	"Oral contraception"	08/11/2000 (inclusion)	Substantial	IAB V versus other progestogen contraceptives	No
MICROVAL (levonorgestrel) CODEPHARMA	Yes	"Oral contraception"	06/09/2000 (re-assessment) 01/10/2008 (RI)	Substantial Substantial		Yes (National Health Insurance only)

*therapeutic category; RI: renewal of inscription.

The tolerance period for forgetting a tablet is 12 hours for CERAZETTE and its generics and 3 hours for MICROVAL.

6.1.2 Other progestogen contraceptives

For information, progestogen contraceptives are used parenterally:

NEXPLANON 68 mg, implant for subdermal use (etonogestrel):

- indication: "Contraception. The safety and efficacy have been established in women between 18 and 40 years of age."
- the implant may be left in place for 3 years,
- reimbursable proprietary medicinal product.

DEPO PROVERA, suspension for injection (deep intramuscular) (medroxyprogesterone)

- indication: "Long-term contraceptive (3 months) when it is not possible to use other contraceptive methods",
- reimbursable proprietary medicinal product.

These progestogens may not be considered as comparators for ANTIGONE.

► Conclusion

The clinically relevant comparators are CERAZETTE and MICROVAL.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Not applicable

08 ANALYSIS OF AVAILABLE DATA

The company has provided six clinical study publications or abstracts.^{3,4,5,6,7,8} Only one publication is considered.⁵ The abstracts are not considered and the studies concerned are those with intermediate efficacy or safety endpoints (inhibition of ovulation, haemostasis tests), the search for dose or efficacy for off-label uses during non-comparative studies: "oestrogen-linked" symptoms (nausea, mastodynia, headache, oedema, dysmenorrhoea).

08.1 Efficacy

The study considered concerns the progestogens desogestrel and levonorgestrel.

Method:

This randomised double-blind study compared the contraceptive efficacy of 75 µg desogestrel with that of 30 µg levonorgestrel. The tablets had to be taken at about the same time every day. The treatment duration was 13 cycles of 28 days. For lactating women, the treatment was initiated at least 28 days after delivery.

Women included were from 18 to 45 years old and had normal cycles of 24 to 35 days. The main non-inclusion criteria were a history of ectopic pregnancy, pelvic inflammatory disease or functional ovarian cysts.

Results:

In all, 989 women were included in the desogestrel group and 331 in the levonorgestrel group. Among them, 979 in the desogestrel group and 327 in the levonorgestrel group started the treatment and were included in the analysis; 540 women in the desogestrel group and 198 in the levonorgestrel group finished the treatment.

Three pregnancies were observed in the desogestrel group and four in the levonorgestrel group, including one ectopic pregnancy, corresponding to a Pearl index (number of pregnancies per 100 women-years) of 0.41, 95% CI: [0.08; 1.2] in the desogestrel group and 1.55, 95% CI: [0.42; 3.96] in the levonorgestrel group.

There was no significant difference between the groups.

³ Rice C, Killick S, Hickling D, Coelingh Bennink H. Ovarian activity and vaginal bleeding with a desogestrel-only preparation at three different doses. 1996. *Human Reprod*; 4: 737-40.

⁴ Rice CF, Killick SR, Dieben T, Coelingh Bennink H. A comparison of the inhibition of ovulation achieved by desogestrel 75 µg and levonorgestrel 30 µg daily. 1999. *Human Reprod*; 4: 982-5.

⁵ Collaborative Study Group on the desogestrel-containing progestogen-only pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 µg/day or levonorgestrel 30 µg/day. *The European Journal of Contraception and Reproductive Health Care*. 1998; 3: 169-78.

⁶ Korver T, Kippling C, Heger-Mahn D, Duijker I, Van Osta G, Dieben T. Maintenance of ovulation inhibition with the 75-microg desogestrel only contraceptive pill (Cerazette) after scheduled 12 h delays in tablet intake. *Contraception*. 2005; 71: 8-13.

⁷ Winkler UH, Howie H, Korver T, Geurts TB, Coelingh Bennink HJ. A randomized controlled double-blind study of the effect on hemostasis of two progestogen-only pills containing 75 microgram desogestrel or 30 microgram levonorgestrel. *Contraception*. 1998; 6: 385-92.

⁸ Ahredt HJ, Karckt U, Pichl T, Mueller T, Ernst U. The effect of an oestrogen-free, desogestrel-containing oral contraceptive in women with cyclical symptoms: results from two studies on oestrogen related symptoms and dysmenorrhoea. *Eur J Contracept Reprod Health Care*. 2007; 4: 354-61.

08.2 Safety/Adverse effects

8.2.1 Clinical study

In the study retained,⁵ treatment discontinuations concerned 439/979 women (44.8%) in the desogestrel group and 129/327 women (39.4%) in the levonorgestrel group.

Treatment discontinuations linked to irregular bleeding concerned 22.5% of women in the desogestrel group and 18% in the levonorgestrel group.

The bleeding profile was analysed by 90-day periods. During the first period (D29-D118), the relative risk of bleeding on desogestrel versus levonorgestrel was 1.75 for infrequent bleeding/spotting (one or two episodes per reference period), 1.56 for frequent bleeding/spotting (six or more episodes per reference period) and 2.14 for extended bleeding/spotting (episode lasting more than 14 days).

During the fourth reference period (D271-D360), about half of women of the desogestrel group and 10% of women of the levonorgestrel group had amenorrhoea or infrequent bleeding. The main adverse events appear in Table 1.

Table 1: adverse events

	desogestrel	levonorgestrel
Adverse events (% of patients)	41.8%	41.3%
Serious adverse events (% of patients)	1.4%	1.8%
Serious adverse events considered to be treatment-related (n).	4*	2†
The most common adverse events (% of patients)‡		
Acne	3.1%	4.0%
Headaches	7.5%	6.1%
Nausea	3.3%	1.5%
Mastodynia	4.0%	3.1%
Dysmenorrhoea	1.2%	3.4%
Vaginitis	3.8%	2.8%

*: ovarian cysts;

†: one ovarian cyst and one ectopic pregnancy

‡: >3% in at least one treatment group

8.2.2 Data from the literature

No data were found in the literature showing an increased risk of venous and arterial thromboembolisms with desogestrel alone relative to no hormonal contraception:

- A Danish cohort study⁹ created from data from four national registries (population, education level, medical prescriptions, hospitalisations with their diagnosis) evaluated the risk of venous thromboembolisms on hormonal contraception. The duration of the study was from January 1995 to December 2005. The study population included 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 the 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 data collected on contraception included the period of use (current, past or none), the means (combined oral contraceptive, oral progestogen only or progestogen-releasing intrauterine system) and the different compositions of progestogen oral contraceptives (30 µg levonorgestrel, 350 µg norethisterone and 75 µg desogestrel).

The analysis was adjusted for age, calendar year and education level.

⁹ Lidegaard O, Lokkegaard E *et al.* Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*, 2009; 339: b2890.

For a follow-up of 9044 women-years, the incidence rate ratio for venous thromboembolic events was 1.10 [95% CI: 0.35; 3.41]. There was no evidence of an increase in this risk on desogestrel 75 µg relative to women not using hormonal contraception:

- A study conducted in Denmark¹⁰ on the same cohort as the previous one sought to evaluate the risk of a first venous thromboembolism on oral contraceptives according to the type of progestogen and the oestrogen dose. This cohort included Danish women from age 15 to 49 between 1995 and 2009. The data collected were from four sources: statistics from Denmark (personal identification number for each citizen), the national patient registry (discharge diagnosis for each hospitalisation), the national registry for causes of death and the national registry for medical products (data on oral contraception prescriptions). Women who had had cancer, a venous or an arterial thromboembolism, a 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, a bilateral oophorectomy, hysterectomy or sterilisation or who had undergone treatment to stimulate ovulation during the study were censored at the time of the diagnosis or intervention; data were also censored during pregnancy and for the first 3 months after childbirth. The data collected on the 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 4 weeks.

The analysis was adjusted for age, education level and calendar year.

For a follow-up of 29,187 women-years and only considering confirmed cases, the relative risk of the occurrence of a venous thromboembolic event was 0.64 [95% CI: 0.29; 1.42]. There was no evidence of an increase in the risk of venous thromboembolic events on desogestrel contraception alone relative to women not using hormonal contraception.

- A meta-analysis¹¹ studied the risk of thromboembolic events in women using contraception by progestogen alone. The relative risk of occurrence of a venous thromboembolic event was 0.90 [95% CI: 0.57; 1.45]. In this meta-analysis, there was no evidence of an association between the venous thromboembolism risk and the use of progestogen oral contraception. One of the studies included in this meta-analysis concerned desogestrel (see previous publication).
- A study conducted in Denmark¹² on the same cohort as the two studies described above aimed to evaluate the risk of ischaemic stroke and myocardial infarction on hormonal contraception. Transient ischaemic accidents were not included in the analysis. Only the first arterial incidents were included. The data were collected from the national patient registry (discharge diagnosis for each hospitalisation), the national registry for causes of death and the national registry for medical products (data on contraception prescriptions). Women who had had cancer, a venous or an arterial thromboembolism, a 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, a bilateral oophorectomy, hysterectomy or sterilisation or who had undergone treatment to stimulate ovulation during the study were censored at the time of the diagnosis or intervention; data were also censored during pregnancy and for the first 3 months after childbirth. Information on cigarette consumption was obtained for 480,223 women, corresponding to 37% of the total follow-up. The analysis was adjusted for age, educational level, calendar year and the existence of risk factors (defined as taking treatments for hypertension, heart disease, diabetes and hyperlipidaemia).

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.

¹¹ Mantha S. *et al.* Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. *BMJ*. 2012; 345: e4944 doi: 10.1136/bmj.e4944.

¹² Lidegaard O *et al.* Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med*. 2012; 366: 2257-66

For a follow-up of 29,185 women-years, the relative risk of occurrence of an ischaemic stroke was RR=1.37 [95% CI: 0.71; 2.63] and that for myocardial infarction was RR=1.46 [95% CI: 0.55; 3.90]. There is therefore no evidence of a significant increase in the risk of arterial thromboembolisms on oral contraception with desogestrel alone relative to women not using hormonal contraception.

These risks were also not significantly increased in contraception by oral norethindrone or levonorgestrel, levonorgestrel-releasing intrauterine system or subdermal implant.

08.3 Summary & discussion

In the only acceptable study, the contraceptive efficacy of 75 µg desogestrel was compared with that of 30 µg levonorgestrel. The Pearl index was 0.41 (95% CI: [0.08; 1.2]) in the desogestrel group and 1.55 (95% CI: [0.42; 3.96]) in the levonorgestrel group. The difference between groups is not statistically significant.

In the desogestrel group relative to levonorgestrel:

- The adverse effects, including serious ones, were of the same order in both groups.
- Treatment discontinuations were more numerous in the desogestrel group, in particular, those related to irregular bleeding (22.5% vs 18%).
- Cycle disruptions were more common in the desogestrel group: frequent/prolonged bleeding and amenorrhoea/oligomenorrhoea.
- The incidence of other adverse events was comparable between the two groups.

No thromboembolic event was reported in this study.

The SPC for ANTIGONE specifies, in the special warnings and precautions for use section: "Epidemiological investigations have associated the use of COCs [combined oral contraceptives] with an increased incidence of venous thrombosis (venous thromboembolism, deep vein thrombosis and pulmonary embolism). Although the clinical relevance of this finding for desogestrel used as a contraceptive in the absence of an oestrogenic component is unknown, ANTIGONE should be discontinued in the event of a thrombosis. Discontinuation of ANTIGONE should also be considered in case of long-term immobilisation due to surgery or illness. Women with a history of venous thromboembolic disorders should be made aware of the possibility of a recurrence."

Epidemiological studies did not show evidence of an increased thromboembolic risk with oral contraceptives containing only a low dose progestogen, whether desogestrel or levonorgestrel relative to no contraception.

However, these medicines are contraindicated in the event of progressive venous thrombosis.

09 THERAPEUTIC USE

The contraceptive method must be suited to each woman and chosen with her, in accordance with her daily life and possible contraindications.¹³

Progestogen oral contraceptives, such as subdermal and injectable progestogen contraceptives, oral vaginal and transdermal oestrogen progestogen contraceptives, copper intrauterine devices and intrauterine systems with levonorgestrel and female sterilisation techniques are among the most effective contraceptive methods available according to the WHO.¹⁴

ANTIGONE is a first-line contraceptive means, especially postpartum, when breastfeeding¹ and in certain situations in women at cardiovascular risk (see HAS memo).²

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- ▶ Access to appropriate contraception for all women who decide to use it is a public health objective,
- ▶ These proprietary medicinal products are a part of preventing unwanted pregnancy,
- ▶ The efficacy/adverse effects ratio for these medicinal products is high.
- ▶ There are contraceptive alternatives,
- ▶ This medicinal product is a first-line medicine,
 - ▶ Public health benefit:
Ensuring access to suitable contraception and reducing the frequency of voluntary terminations of pregnancy are public health objectives defined by the GTNDO [National Technical Group for the Definition of Public-Health Objectives].
There is therefore a public health need, but the response to this need cannot be reduced to reimbursement for new oral contraceptives alone.
Given that there are alternatives, it is not expected that ANTIGONE 75 will benefit public health.

Taking account of these points, the Committee considers that the actual benefit of ANTIGONE 75 is substantial in the Marketing Authorisation indication.

010.2 Improvement in actual benefit (IAB)

ANTIGONE 75 does not provide an improvement in actual benefit (IAB V, non-existent) in the management of contraception.

¹³ HAS - memo sheet – contraception: prescription et conseil chez la femme (version du 28/02/2013) [contraception: prescription and advice for women (version of 28/02/2013)].

¹⁴ HAS - summary document - Méthodes contraceptives : [contraceptive methods:] Focus on the most effective methods available - March 2013, updated September 2013

010.3 Target population

The proportion of women using low-dose progestogen oral contraception among women using contraception is not known.¹⁵

For information, sales of progestogen minipills in 2012 (GERS [Partnership to Collect and Prepare Statistics] data) were 3,244,789 boxes.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication "contraception" and at the dosages in the Marketing Authorisation.

► **Proposed reimbursement rate: 65%**

► **Packaging**

Appropriate for the prescribing conditions as regards the indication, dosage and treatment duration.

¹⁵ Bajos N, Bohet A, Le Guen M, Moreau C. La contraception en France : nouveau contexte, nouvelles pratiques? INED [National Institute for Demographic Studies] - Populations & Sociétés - No. 492 - September 2012