**TRANSPARENCY COMMITTEE**

Opinion

17 September 2014

**VEREGEN 10%, ointment**

**Tube of 15 g (CIP: 34009 222 531 2 1)**

Applicant: EXPANSCIENCE

<table>
<thead>
<tr>
<th>INN</th>
<th>Dry extract of green tea leaf <em>Camellia sinensis</em> (L.) O. Kuntze</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC Code (2013)</td>
<td>D06BB12 (antiviral)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>Lists concerned</td>
<td>National Health Insurance (French Social Security Code L.162-17)</td>
</tr>
<tr>
<td></td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>“VEREGEN is indicated for the cutaneous treatment of external genital and perianal warts (<em>condylomata acuminata</em>) in immunocompetent patients from the age of 18 years.”</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Insufficient</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Improvement in Actual Benefit</td>
<td>N/A</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>In view of the low level of effect of VEREGEN 10% on external genital and perianal warts relative to placebo in immunocompetent patients, its conditions of use, which are more onerous than those of the proprietary medicinal products already available, and the existence of treatment alternatives, VEREGEN 10% does not have a role in the therapeutic strategy for condylomata acuminata in immunocompetent adults.</td>
</tr>
</tbody>
</table>
**01 ADMINISTRATIVE AND REGULATORY INFORMATION**

<table>
<thead>
<tr>
<th>Marketing Authorisation</th>
<th>Initial date: 25/06/2012 (mutual recognition procedure, rapporteur country: Germany)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Because of a change to the raw drug/native extract ratio of the plant-based product used for VEREGEN 10% ointment, a request for the extension of the Marketing Authorisation was submitted on 11/02/2013 within the framework of the European Marketing Authorisation procedure. This change did not lead to any alteration of the level of catechins in the extract of green tea and in VEREGEN ointment. Notification of the amendment of the Marketing Authorisation was issued by the ANSM [French National Agency for Medicines and Health Products Safety] on 27 February 2014.</td>
</tr>
</tbody>
</table>

**Risk Management Plan**

| Prescribing and dispensing conditions | List I of toxic substances |

<table>
<thead>
<tr>
<th>ATC Classification</th>
<th>2013</th>
<th>D</th>
<th>Dermatologicaless</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D06</td>
<td>Antibiotics and chemotherapeutics for dermatological use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D06B</td>
<td>Chemotherapeutics for topical use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D06BB</td>
<td>Antivirals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>D06BB12</td>
<td>Sinecatechins</td>
<td></td>
</tr>
</tbody>
</table>

**02 BACKGROUND**

The company is requesting inclusion of VEREGEN 10% ointment on the list of medicines refundable by National Health Insurance and/or on the list of medicines approved for hospital use in the cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years.

Its active ingredient is a refined dry extract for green tea leaf, *Camellia sinensis* (L.) O. Kuntze, containing 85 to 95% sinecatechins, mainly (-)-epigallocatechin gallate.

**03 THERAPEUTIC INDICATION**

“VEREGEN is indicated for the cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years.”
**04 DOSAGE**

“In adults, up to 250 mg VEREGEN ointment per single dose, corresponding to about 0.5 cm of ointment strand, to be applied three times daily to all external genital and perianal warts (750 mg total daily dose).

**Duration of use**
Treatment with VEREGEN should be continued until complete clearance of all warts, however, no longer than 16 weeks in total (max. duration), even if new warts develop during the treatment period.

**Paediatric population**
The safety and efficacy of VEREGEN in children and adolescents below the age of 18 years have not been investigated. No data are available.

**Older people**
An insufficient number of older people were treated with VEREGEN ointment to determine whether they react differently from younger subjects.

**Patients with hepatic impairment**
Patients with severe liver dysfunction (e.g. clinically relevant elevation of liver enzymes, increase of bilirubin, increase of INR) should not use VEREGEN due to insufficient safety data.”

**05 THERAPEUTIC NEED**

External condylomata are benign tumours of low oncogenic risk associated in 90% of cases with human *papillomavirus* (HPV 6 et 11).\(^1\) In the vast majority of cases, they are localised in the external genital region, and less often in the perianal region.\(^2\)

HPV infections are the most common sexually transmissible infections (3 to 5% of the general population will present clinical lesions; 10 to 15% a latent infection). The course is most often characterised by an increase in the number and size of the lesions, leading to physical and psychological discomfort, and in 20 to 30% of cases spontaneous regression occurs.\(^2\) The risk of the development of a cancerous lesion (in the anogenital region) is due to the persistence of an associated latent HPV oncogene (in the case of multi-infection) and not to malignant changes in these lesions.

The objective of treatment is the disappearance of visible lesions. The following types of treatment are available:
- physical and surgical treatments, that is to say cryotherapy, electrocoagulation, CO\(_2\) laser treatment, and surgical excision,
- an immunomodulatory treatment based on imiquimod (ALDARA),
- chemical treatments based on podophyllotoxin (CONDYLINE), 5-fluorouracil (EFUDIX) or trichloroacetic acid.\(^2\)

No treatment currently available eradicates the papillomavirus that is present in the body.

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There is a vaccine for the prevention of condylomata acuminata, the quadrivalent vaccine covering HPV genotypes 6, 11, 16 and 18 (GARDASIL), indicated in the prevention of high-grade cervical dysplasias, cervical cancers and condylomata acuminata.

Contraceptives are not considered useful in the prevention of infection, as they are insufficiently effective, since penetration with the penis is not necessary for infection of the sexual partner and close sexual contact is a typical mode of infection.

It should be noted that, according to the SPC for VEREGEN 10%, the mechanism of action of sinecatechins in the treatment of external genital and perianal warts is not known.
## CLINICALLY RELEVANT COMPARATORS

### 06.1 Medicinal products

The comparator drugs for VEREGEN 10% are medicinal products used in the treatment of genital or perianal warts:

<table>
<thead>
<tr>
<th>Name (INN)</th>
<th>Company</th>
<th>Same TC</th>
<th>Indications</th>
<th>Date of Opinion</th>
<th>Actual Benefit</th>
<th>Improvement in Actual Benefit (wording)</th>
<th>Reimbursed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDARA 5% (Imiquimod)</td>
<td>Meda Pharma</td>
<td>Yes</td>
<td>Topical treatment of external genital and perianal warts (condylomata acuminata) in adults</td>
<td>03/11/1999 (inclusion) 13/04/2005 (RI) 10/03/2010 (RI)</td>
<td>substantial</td>
<td>IAB IV in terms of ease of use (1 application per day instead of 2 applications/day) compared with CONDYLINE solution for local application.</td>
<td>yes</td>
</tr>
<tr>
<td>CONDYLINE 0.5% (podo-phyllotoxin)</td>
<td>Astellas Pharma SAS</td>
<td>Yes</td>
<td>Condylomata acuminata with an area of less than 4 cm², as an alternative to other techniques (cryotherapy, surgical methods, etc.)</td>
<td>26/11/2008 (RI) 05/02/2014 (RI)</td>
<td>substantial</td>
<td>-</td>
<td>yes</td>
</tr>
<tr>
<td>EFUDIX 5% (5-fluorouracil)</td>
<td>Meda Pharma</td>
<td>No</td>
<td>Genital condylomata.</td>
<td>15/02/2006 (RI) 22/09/2010 (RI)</td>
<td>substantial</td>
<td>-</td>
<td>yes</td>
</tr>
</tbody>
</table>

SCT: Pharmacotherapeutic class  
RI: Renewal of Inclusion  

NB: ALDARA, CONDYLINE and EFUDIX may be used in immunocompetent patients and in immunocompromised patients as well.  
Another chemical treatment is available: trichloroacetic acid. This karatolytic agent does not have Marketing Authorisation and must be applied by a physician.

### 06.2 Other health technologies

Other treatments are available, physical and surgical treatments, that is to say cryotherapy, electrocoagulation, CO₂ laser treatment, and surgical excision.

> **Conclusion**  
The comparators listed are all clinically relevant.
Since 2006, VEREGEN 15% has had Marketing Authorisation in the United States.
Initial Marketing Authorisation for VEREGEN 10% was granted in Germany (Reference Member State) in August 2009, in Austria in February 2010, and in Spain in February 2011 by the decentralised procedure.
Since March 2012, VEREGEN 10% has had Marketing Authorisation in 17 European countries, including France. In June 2014, 7 European countries decided to reimburse.

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Population(s) Marketing Authorisation or restricted population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES/NO</td>
<td>If no, why not</td>
</tr>
<tr>
<td>Germany</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Austria</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Belgium</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>Assessment in progress</td>
<td>NA</td>
</tr>
<tr>
<td>Cyprus</td>
<td>Assessment in progress</td>
<td>NA</td>
</tr>
<tr>
<td>Denmark</td>
<td>NO (efficacy not demonstrated)</td>
<td>NA</td>
</tr>
<tr>
<td>Spain</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Finland</td>
<td>NO (efficacy not demonstrated)</td>
<td>NA</td>
</tr>
<tr>
<td>Greece</td>
<td>Assessment in progress</td>
<td>NA</td>
</tr>
<tr>
<td>Hungary</td>
<td>NO (conformity with other topicals with the same indication)</td>
<td>NA</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Norway</td>
<td>NO (efficacy not demonstrated)</td>
<td>NA</td>
</tr>
<tr>
<td>Netherlands</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Poland</td>
<td>NO (conformity with other topicals with the same indication)</td>
<td>NA</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>NO (conformity with other topicals with the same indication)</td>
<td>NA</td>
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<tr>
<td>Romania</td>
<td>Assessment in progress</td>
<td>NA</td>
</tr>
<tr>
<td>Slovakia</td>
<td>Assessment in progress</td>
<td>NA</td>
</tr>
<tr>
<td>Slovenia</td>
<td>YES</td>
<td>MA population</td>
</tr>
<tr>
<td>Sweden</td>
<td>NO (efficacy not demonstrated)</td>
<td>NA</td>
</tr>
<tr>
<td>Switzerland</td>
<td>YES</td>
<td>MA population</td>
</tr>
</tbody>
</table>
08 ANALYSIS OF AVAILABLE DATA

For this application for inclusion, the company provided data from two phase III, randomised, double-blind studies (CT-1017 and CT-1018) versus placebo.\(^3\)\(^4\)

08.1 Efficacy

8.1.1 Studies CT-1017 and CT-1018\(^3\)\(^4\)

Studies CT-1017 and CT-1018 are phase III, randomised, double-blind, multicentre, parallel group, placebo-controlled studies.
As a reminder, only the 10% dosage has been granted Marketing Authorisation in France. The results relating to VEREGEN 15% are not, therefore, presented in this document.

Method:

Table 1: Methods used in studies CT-1017 and CT-1018

<table>
<thead>
<tr>
<th>Dates and study locations</th>
<th>Study CT-1017</th>
<th>Study CT-1018</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 centres in Europe and South Africa, between September 2002 and December 2003.</td>
<td>50 centres in North, Central and South America and also in Romania, between July 2003 and August 2004.</td>
<td></td>
</tr>
</tbody>
</table>

| Primary objective | Evaluation of the efficacy of VEREGEN 10% and 15% versus placebo in the treatment of condylomata acuminata in adult patients for a period not exceeding 16 weeks |

| Inclusion criteria | - Patients aged at least 18 years  
- Diagnosed with condylomata acuminata that can be located:  
  - In men: on the glans, the penis, the scrotum, or the prepubice;  
  - In women: on the vulva  
  - In all patients: in the inguinal, perineal and perianal regions;  
- Presence of 2 to 30 condylomata acuminata with an affected area between 12 and 600 mm\(^2\). |

| Main non-inclusion criteria | - Treatment of the condylomata acuminata during the 30 days preceding randomisation;  
- Treatment with virostatics by the systemic route during the 30 days preceding randomisation and for the duration of the study, with the exception of aciclovir and its derivatives (famciclovir and valaciclovir);  
- Treatment with immunosuppressants (interferons) during the 30 days preceding randomisation and for the duration of the study;  
- \textit{Herpes genitalis} infection requiring topical treatment;  
- Genital infections other than condylomata acuminata or infections not successfully treated within the preceding 30 days;  
- Patients with viral hepatitis B or C (chronic or acute infection) or HIV;  
- Pregnancy or breastfeeding |

| Administered treatments | The patients were randomised into three treatment groups at a ratio of 2:2:1:  
- VEREGEN 10%, ointment  
- VEREGEN 15%, ointment  
- Placebo ointment |

The treatment was applied to the condylomata acuminata 3 times daily at 8 hour intervals, with a dosage of less than 250 mg per application for a maximum duration of treatment of 16 weeks (except in the event of confirmed complete disappearance before the end of the 16 weeks). In the event of complete disappearance of the condylomata acuminata in the course of treatment or after 16 weeks of treatment, a follow-up visit was planned four weeks later. In the absence of recurrence or of new lesions, follow-up was continued for an additional 8 weeks.


Primary efficacy endpoint
Percentage of patients with complete disappearance of all condylomata acuminata (condylomata that were present at inclusion and those that appeared during the treatment phase) during the maximum period of treatment (16 weeks).

Secondary endpoints
- Percentage of patients with complete disappearance of the condylomata acuminata that were present at inclusion during the treatment period;
- Percentage of patients with new condylomata acuminata during the 16 week treatment period (which were not present at inclusion) and during the 12 week follow-up period (corresponding neither to condylomata present at inclusion nor those that appeared during the treatment period);
- Percentage of patients with complete disappearance of the condylomata acuminata that were present at inclusion or that appeared during the treatment period and who showed recurrence during the 12 week follow-up period. Recurrence includes reappearance of condylomata that had disappeared after treatment and those that appeared during the treatment period;
- Time taken for complete disappearance of the condylomata acuminata during the treatment period (condylomata that were present at inclusion or those that appeared during the treatment period).

Calculation of the number of subjects required
Assuming:
- a randomisation ratio of 2:2:1,
- a difference of 20% between VEREGEN 10% and placebo in terms of the levels of complete disappearance,
- and a difference of 30% between VEREGEN 15% and placebo in terms of the levels of complete disappearance,
it would be sufficient to include 192 patients in each of the active treatment groups (VEREGEN 10% and VEREGEN 15%) and 96 patients in the placebo group to compare each active treatment with placebo with a power of at least 80% (Fisher’s exact test, two-tailed, $\alpha = 5\%$).

Thus, a total of 480 patients were required in each of the two studies.

Statistical methods used
The analysis of efficacy on the basis of the primary efficacy endpoint was carried out on the basis of the intention to treat (ITT) population and of the per-protocol (PP) population. Each treatment group was compared with the placebo group using Fisher’s exact two-tailed test with correction of the $\alpha$ error risk by Hochberg’s method.

In accordance with the method of handling missing data, 2 variants of the analyses of the ITT population were used:
- **LOCF** (last observation carried forward) analysis including all randomised patients who were given treatment, with an evaluation of the primary endpoint at inclusion and at least one evaluation of the same criterion post inclusion,
- “**Observed cases**” analysis including all randomised patients who were given treatment, who displayed complete disappearance of the condylomata acuminata (present at inclusion or that appeared during the treatment period) during the treatment phase or those that completed the 16 weeks of treatment.

The German Federal Institute for Drugs and Medical devices (BfArM) requested a third statistical analysis of the primary efficacy endpoint: **ITT-LOCF-MR analysis** in which the missing data were considered “absence of complete disappearance”.

Results of study CT-1017:

Treatment exposure
A total of 503 patients were included, with:
- 199 patients in the VEREGEN 10% group,
- 201 patients in the VEREGEN 15% group,
- 103 patients in the placebo group.

Of the patients included, 18.3% discontinued treatment prematurely ($n=92$). The discontinuations of treatment were similar in the different treatment groups. They were mainly due to withdrawal of consent (38.0%), failure to conform with the study procedures (16.3%), and lack of efficacy (15.2%).
Patient characteristics on inclusion
On inclusion, the characteristics of the patients in the different treatment groups were comparable. The average age of the patients was 30.7 years (± 10.9), and the proportion of men was 55.1%. The majority of the women (88.9%) were of reproductive age, and 9.4% of the men had been circumcised.

The locations of the condylomata were homogeneous across the treatment groups:
- among the men, mainly on the body of the penis (65%), the glans (24.2%), the foreskin (19.5%) and the perianal region (12.3%);
- among the women, mainly on the vulva (84.1%), the perianal region (21.7%) and the perineum (17.7%).

All the patients had already had at least one previous episode of genital warts. The intervals between the time of the first diagnosis, the present episode, and the inclusion visit were comparable in the active treatment groups. The mean period between the onset of the present episode and the start of treatment was similar in the active treatment groups and in the placebo group.

Efficacy with respect to the primary efficacy endpoint (complete disappearance of the condylomata acuminata that were present at inclusion and those that appeared during the treatment phase)
A difference in the response between the VEREGEN 10% group and the placebo group in favour of the VEREGEN group was observed, but not in the “observed cases” analysis:
- In the LOCF analysis, the percentage of patients with complete disappearance of all condylomata acuminata was higher in the VEREGEN 10% group (50.8%) than in the placebo group (37.3%) (p=0.028).
- In the “observed cases” analysis, there was no difference between the percentage of patients with complete disappearance of all condylomata acuminata in the VEREGEN 10% group (57.2%) and the placebo group (46.3%) (p=0.109).

The proportion of missing data was 13% in the VEREGEN 10% group and 20% in the placebo group.
- In the LOCF-MR analysis (where the missing data that were not taken into account in the LOCF and “observed cases” analyses were considered as failures4), the percentage of patients with complete disappearance of all condylomata acuminata was higher in the VEREGEN 10% group (49.7%) than in the placebo group (36.9%) (p=0.038).

It should be noted that the level of complete disappearance among the women was higher than among the men in all three types of analysis.

Efficacy with respect to the secondary endpoints (LOCF analysis only)
Over the course of the treatment period, the percentage of patients with complete disappearance of the condylomata present at inclusion was higher under VEREGEN 10% (52.3%) than under placebo (39.2%) (p<0.001).

The total level of disappearance of all condylomata was 50.8% under VEREGEN 10% versus 37.3% under placebo. The difference between the levels of partial disappearance in the VEREGEN 10% group and the placebo group favoured VEREGEN 10%, with 18.5% versus 7.8% of patients displaying a level of reduction of all condylomata between 75 and 99% (p=0.001).

There was no difference between the percentage of patients who developed new condylomata during the treatment period in the VEREGEN 10% group (42.2%) and in the placebo group (34%) (p=0.15).

In the course of the follow-up period, 4.1% (4/98) of the patients who had been treated with VEREGEN 10% had a recurrence, versus 2.6% (1/38) under placebo (p not determined).

4 4 missing data in the VEREGEN 10% group and 1 in the placebo group.
In the course of the follow-up period, 5.1% (5/98) of the patients who had been treated with Veregén 10% developed new condylomata, versus none under placebo (p not determined).

No difference between the median period until disappearance of all condylomata (those present at inclusion and those that developed in the course of the treatment period) under Veregén 10% (16.4 weeks or 115 days) and placebo (16.7 weeks or 117 days) was observed (p=0.12).

It should be noted that Veregén, like its comparators, does not eradicate human papillomavirus. Thus, the evaluation of its efficacy on the basis of recurrence and the appearance of new condylomata during the follow-up period should be interpreted with caution.

**Results of study CT-1018:**

**Treatment exposure**
A total of 502 patients were included, with:
- 202 patients in the Veregén 10% group,
- 196 patients in the Veregén 15% group,
- 104 patients in the placebo group.

Of the patients included, 19.5% discontinued treatment prematurely (n=98). The discontinuations of treatment were mainly due to withdrawal of consent (6.6%), lack of efficacy (3.4%), and failure to conform with the study procedures (2.8%).

**Patient characteristics on inclusion**
On inclusion, the characteristics of the patients in the different treatment groups were comparable. The average age of the patients was 31.5 years (± 12.1), and the proportion of men was 51.4%. The majority of the women (80.3%) were of reproductive age, and 20.9% of the men had been circumcised.

The locations of the condylomata were homogeneous across the treatment groups:
- among the men, mainly on the body of the penis (71%) and the glans (22.8%);
- among the women, on the vulva (84.8%);
- among the men and the women, in the perianal zone (15.3%) and in the perineum (18.1%).

All the patients had already had at least one previous episode of genital warts. The interval between the time of the first diagnosis, the present episode, and the inclusion visit was comparable in the active treatment groups. The mean period between the onset of the present episode and the start of treatment was similar in the active treatment groups and in the placebo group.

**Efficacy with respect to the primary efficacy endpoint (complete disappearance of the condylomata acuminata that were present at inclusion and those that appeared during the treatment phase)**
A difference in response between the Veregén 10% group and the placebo group favouring Veregén 10% was observed in the three types of analysis:
- In the LOCF analysis, the percentage of patients with complete disappearance of all condylomata acuminata was higher in the Veregén 10% group (56.3%) than in the placebo group (33.7%) (p<0.001).
- In the “observed cases” analysis, the percentage of patients with complete disappearance of all condylomata acuminata was higher in the Veregén 10% group (64.2%) than in the placebo group (42.2%) (p=0.001).

The proportion of missing data was 14% in the Veregén 10% group, 16% in the Veregén 15% group and 20% in the placebo group.
- In the LOCF-MR analysis (where the missing data that were not taken into account in the LOCF and “observed cases” analyses were considered as failures\(^5\)), the percentage of patients with

\(^5\) 5 missing data in the Veregén 10% group and none in the placebo group.
complete disappearance of all condylomata acuminata was higher in the VEREGEN 10% group (55.0%) than in the placebo group (33.7%) (p<0.001).

It should be noted that the level of complete disappearance among the women was higher than among the men in all treatment groups.

Secondary endpoints (LOCF analysis only)
Over the course of the treatment period, the percentage of patients with complete disappearance of the condylomata present at inclusion was higher under VEREGEN 10% (60.9%) than under placebo (33.7%) (p<0.001).

The total level of disappearance of all condylomata was 56.6% under VEREGEN 10% versus 34% under placebo. The proportion of subjects with between 50 and 75% partial disappearance of all condylomata appears higher in the VEREGEN 10% group (8.2%) than in the placebo group (3.9%). However, the proportion of subjects with between 75 and 99% partial disappearance of all condylomata appears lower in the VEREGEN 10% group (9.2%) than in the placebo group (13.6%) (p not determined).

There was no difference between the percentage of patients who developed new condylomata during the treatment period in the VEREGEN 10% group (41.6%) and the placebo group (46.2%) (p=0.85).

In the course of the follow-up period, 8.3% of the patients who had been treated with VEREGEN 10% had a recurrence, versus 8.8% who received placebo (p not determined).

In the course of the follow-up period, 7.9% of the patients who had been treated with VEREGEN 10% developed new condylomata, versus none of the patients in the placebo group (p not determined).

The period until disappearance of all condylomata occurred was shorter in the VEREGEN 10% group (16.1 weeks or 113 days) than in the placebo group (16.9 weeks or 118 days) (p<0.001).

It should be noted that VEREGEN 10%, like all its comparators, does not eradicate human papillomavirus; the evaluation of its efficacy on the basis of recurrence and the appearance of new condylomata during the follow-up period should be interpreted with caution.

8.1.2 Pooled analysis of studies CT-1017 and CT-1018
A pooled analysis based on the data from the two studies CT-1017 and CT-1018 has been performed. In relation to the primary efficacy endpoint, the proportion of patients with complete disappearance of all condylomata acuminata was higher in the VEREGEN 10% group than in the placebo group in ITT LOCF (53.6% versus 34.4%; p<0.001), in ITT “observed cases” (60.7% versus 44.2%; p<0.001) and in ITT LOCF-MR (52.4% versus 35.3%; p<0.001).

08.2 Adverse Effects
8.2.1 Data from clinical studies

Study CT-1017
A total of 399 patients received at least one application of VEREGEN, 198 of them VEREGEN 10% and 201 of them VEREGEN 15%.

The median duration of treatment was similar in the three groups (112 days).

The percentage of patients with at least one adverse event (AE) was 23.7% under VEREGEN 10% (n=47) and 21.4% under placebo (n=22). The majority of the events (87%) were mild to moderate. No treatment-related serious adverse events (SAE) were reported under VEREGEN 10% or under placebo.
During the treatment phase, 81.5% of patients under VEREGEN 10% and 61.8% under placebo presented a local reaction. The most frequent reaction was erythema. The proportion of patients under VEREGEN 10% who had at least one severe local reaction was 13.3%, and under placebo it was 1.9%. No deaths were reported during the study.

**Study CT-1018**
A total of 398 patients received at least one application of VEREGEN, 202 of them VEREGEN 10% and 196 of them VEREGEN 15%. The median duration of treatment was 99 days in the VEREGEN 10% group and 112 days in the placebo group.

The percentage of patients with at least one adverse event (AE) was 43.1% under VEREGEN 10% (n=87) and 38.5% under placebo (n=40). The majority (86%) of the adverse events were mild to moderate. One serious adverse event (SAE) deemed to be treatment-related was reported under VEREGEN 10% (pustular vaginitis) and none under placebo. During the treatment phase, 83.3% of patients under VEREGEN 10% and 72.1% under placebo presented a local reaction. The proportion of patients under VEREGEN 10% who had at least one severe local reaction was 41.1%, and under placebo it was 6.7%. No deaths were reported during the study.

8.2.2 PSUR data
Between the start of marketing of VEREGEN (in 2007 in the United States) and December 2012, 114 AEs had been reported, 95 of them considered serious. The main AEs reported were:
- skin reactions, most often at the site of application (pain, pruritus, discoloration, erythema, oedema, induration, vesicular eruption) sometimes accompanied by local infections,
- an increase in the condyloma lesions in the first few weeks of treatment.

The serious AEs most often reported were:
- reactions at the application site (ulceration of the skin, irritation of the skin and dermatitis),
- infections: mycosis or genital herpes.

Six cases of genital herpes have been reported so far, two of them serious.

8.2.3 SPC data
The adverse events cited in the SPC agree with those described in the PSUR. Very common adverse events (> 1/10) are: “local reactions at the site of application like erythema, pruritus, irritation/burning, pain, ulcer, oedema, induration and vesicles”.
Common adverse effects (≥ 1/100 to < 1/10) are: “local reactions at the site of application like exfoliation, discharge, bleeding and swelling, inguinal lymphadenopathy and phimosis”.

However, no adverse events have been reported in the literature.
08.3 Summary and discussion

The efficacy and safety of VEREGEN 10% have been compared with placebo in two randomised, double-blind phase III studies (CT-1017 and CT-1018) in 1005 patients presenting between 2 and 30 external condylomata acuminata with an affected area between 12 and 600 mm$^2$ (401 in the VEREGEN 10% group, 397 in the VEREGEN 15% group and 207 in the placebo group).

On average, the patients were 31 years old, the proportion of men in the 3 treatment groups was slightly higher than that of women (between 52 and 57%). Overall, 84% of the women were of reproductive age, and 15% of the men had been circumcised.

The population included corresponded to the patients targeted by the indication and the duration of treatment corresponded to that recommended in the SPC. The duration of follow-up (12 weeks) was appropriate, because it corresponded to the period with the highest risk of recurrence. The percentages of trial dropouts were high in both the studies: 18.3% (CT-1017) and 19.5% (CT-1018).

Results for the primary efficacy endpoint
The percentage of subjects with complete disappearance of all condylomata acuminata (those present at inclusion and those that appeared during treatment) was higher in the VEREGEN 10% group than in the placebo group.

In ITT-LOCF:
- in study CT-1017: 50.8% of the patients under VEREGEN 10% versus 37.3% under placebo showed complete disappearance of all condylomata (p=0.028).
- in study CT-1018: 56.3% of the patients under VEREGEN 10% versus 33.7% under placebo showed complete disappearance of all condylomata (p<0.001).

The level of the effect of VEREGEN 10% is small, in that one patient in two (between 50.8% and 56.3%) in the VEREGEN 10% group showed complete disappearance of all condylomata acuminata compared with one patient in three (between 33.7% and 37.3%) in the placebo group. Furthermore, in study CT-1017, the difference between the levels of complete disappearance of all condylomata acuminata under VEREGEN 10% and under placebo (between 10.9 and 13.5%) was less than that envisaged in the calculation of the number of subjects required (20%), irrespective of the type of analysis.

Results for some of the secondary endpoints:
The percentage of patients with complete disappearance of the condylomata acuminata already present at inclusion after 16 weeks of treatment was higher among patients under VEREGEN 10% than among those under placebo.

However, the level of the effect of VEREGEN 10% (between 52 and 61% of patients showed complete disappearance of the condylomata acuminata already present at inclusion) compared with placebo (between 34 and 39%) is low.

The median period until disappearance of all the condylomata was shorter under VEREGEN 10% than under placebo (p<0.001). However, the difference in the period (about 5 days) was not clinically relevant.

It should be noted that the onerous conditions of use (3 applications per day every day of the week for a maximum of 16 weeks) are likely to reduce treatment compliance under VEREGEN 10%, and thus its efficacy under actual conditions of use.

In addition, the studies were carried out against placebo, they do not permit the positioning of VEREGEN 10% within the therapeutic strategy.

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7 Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2010 Vol. 59 / No. RR-12.
In terms of safety, the majority of adverse events observed in the clinical trials and reported in the PSUR were mild or moderate. The main adverse effects are reactions at the site of application (pain, pruritus, discoloration, erythema, oedema, induration, vesicular eruption, ulceration of the skin, dermatitis) sometimes accompanied by local infections.

08.4 Planned studies

No studies with VEREGEN are underway in this indication.

09 THERAPEUTIC USE

The European\textsuperscript{8} and American\textsuperscript{9} guidelines classify treatments for condylomata in two categories:
- treatments performed by the physician (surgery, CO\textsubscript{2} laser, cryotherapy, electrocoagulation, trichloroacetic acid),
- treatments applied by the patient (imiquimod ALDARA, podophyllotoxin CONDYLINE). The proprietary medicinal products ALDARA and CONDYLINE, unlike VEREGEN 10\%, are also indicated in immunocompromised adults.

The majority of condylomata acuminata require one of these treatments, which may be used for a primary infection or in case of recurrence.

Even though surgical treatments are more effective than treatments applied by the patient, none of the treatments leads to a complete cure of condylomata acuminata.\textsuperscript{10}

Thus, the choice of treatment depends on the size, number, morphology and location of the condylomata, but also on the wishes of the patient and the experience of the physician.\textsuperscript{7}

At present, there is no consensus in France about the therapeutic strategy for condylomata acuminata.\textsuperscript{11}

Since there is no study that directly compares VEREGEN 10\% with other treatments applied by the patient, it is not currently possible to position the former relative to the latter.

The method of application of VEREGEN 10\% is more onerous than those of the other treatments that can be applied by the patient, as VEREGEN 10\% needs to be applied 3 times a day every day of the week for a maximum of 16 weeks, whereas ALDARA needs to be applied once daily 3 times a week for a maximum of 16 weeks and CONDYLINE twice a day on three consecutive days of the week for a maximum of 5 weeks.

In view of the low level of effect of VEREGEN 10\% on external genital and perianal warts, compared with placebo in immunocompetent patients, its conditions of use, which are more onerous than those of the proprietary medicinal products already available, and the existence of treatment alternatives, VEREGEN 10\% does not have a role in the therapeutic strategy for condylomata acuminata in immunocompetent adults.


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

010.1 Actual benefit

- External genital and perianal warts (condylomata acuminata) in adults are due to a sexually transmissible viral infection. The persistence of the lesions leads to physical and psychological discomfort, and makes infection of the sexual partner more likely.
- This proprietary medicinal product is intended as curative therapy.
- The efficacy/adverse effects ratio is low.
- There are medicinal and non-medicinal treatment alternatives.
- VEREGEN 10% does not have a role in the therapeutic strategy for condylomata acuminata in immunocompetent adults.

- Public health benefit:
  The current annual incidence and prevalence of condylomata acuminata in France are difficult to estimate. In a publication from 2002, the annual incidence was estimated at 107 new cases per 100,000 inhabitants. Condylomata acuminata, while not life-threatening for patients, have a considerable impact on their quality of life. The public health burden of condylomata acuminata is thus low to moderate.
  Based on the available data, the impact of VEREGEN 10% on morbidity due to condylomata acuminata is insufficient, bearing in mind the low benefit relative to placebo and the risk of poor compliance due to the onerous method of use.
  The transferability of the data to current clinical practice is good, as the populations studied are representative of the affected population.
  Therefore, VEREGEN 10% does not provide a response to an identified public health need.
  Overall, it is not expected that VEREGEN 10% will have an impact on public health in condylomata acuminata in immunocompetent adults.

Taking account of these points, the Committee considers that the actual benefit of VEREGEN 10% is insufficient in the Marketing Authorisation indication.

The Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication “cutaneous treatment of external genital and perianal warts (condylomata acuminata) in immunocompetent patients from the age of 18 years” and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

N/A

010.3 Target population

N/A

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