NICE advice

External genital and perianal warts: green tea (Camellia sinensis) leaf extract 10% ointment

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in December 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Green tea (*Camellia sinensis*) leaf extract 10% ointment (Catephen) is a self-administered topical treatment for external genital and perianal warts. In 2 randomised controlled trials (RCTs) involving a total of 1005 adults, green tea leaf extract 10% ointment was 2-fold more effective than vehicle (placebo) ointment in terms of complete clearance of all baseline and new warts over a maximum treatment duration of 16 weeks. Most reported

adverse events were local skin reactions, and were mild or moderate in severity. There are no published comparisons with other active treatments for genital and perianal warts.

Regulatory status: Catephen 10% ointment was launched in the UK in November 2015.

Effectiveness	**Safety**
• In 2 RCTs (n=1005), up to 16 weeks, statistically significantly more people using green tea leaf extract 10% ointment had complete clearance of warts compared with vehicle (53.6% and 35.4% respectively, p<0.001). • Over a 12-week follow-up phase, recurrence rates were low (approximately 6%), with no statistically significant difference between the groups. Recurrence rates beyond 12 weeks are not known.	• In the 2 RCTs, local skin reactions were reported by 82.9% of participants using green tea leaf extract 10% ointment and 60.4% using vehicle (no statistical analysis reported). • Severe local reactions were more common in the active treatment group (27.4%) compared with the vehicle group (4.4%), although very few people discontinued treatment due to adverse effects. • The summary of product characteristics states that local reactions at the application site, such as redness, itching and burning, occur in at least 1 in 10 people. • The maximum duration of treatment for the ointment is 16 weeks; the safety profile beyond this time period is not known.

Patient factors	Resource implications
• UK national guidelines on the management of anogenital warts state that treatment decisions should be made only after discussing the appropriate options with the person. • There are 3 self-administered topical treatment options for external genital and perianal warts. All can cause local skin reactions. • The maximum treatment duration for green tea leaf extract ointment is 16 weeks, with application 3 times a day. The maximum duration ranges from 4 to 5 weeks for podophyllotoxin preparations to 16 weeks for imiquimod 5% cream. These treatments require less frequent administration than green tea leaf extract ointment. • These 3 treatments are available in a variety of formulations and may vary in their ease of application.	• As well as the unit cost, the cost of treatments for anogenital warts is dependent on the size of the area treated and the duration required. • Green tea leaf extract 10% ointment (Catephen) is available in a 15 g tube, costing £39.00 (MIMS, November 2015). • The maximum cost per treatment course for green tea leaf extract 10% ointment is £234. • Imiquimod 5% cream costs up to £194.40 per treatment course and podophyllotoxin-based products cost approximately £15 per treatment course.

Introduction and current guidance

Anogenital warts (*condylomata acuminata*) are benign, proliferative growths caused by human papillomavirus (HPV). They are 1 of the most common conditions treated in genitourinary medicine (sexual health) clinics, with over 130,000 cases treated each year in the UK.

Treatment choice in genital warts is influenced by the number and size of warts, location of warts, gender and degree of skin keratinisation. Treatment options recommended by the British Association for Sexual Health and HIV (BASHH) in their UK national guidelines on the management of anogenital warts include self-applied treatments (podophyllotoxin

0.5% solution or 0.15% cream, imiquimod 5% cream and green tea leaf extract 10%) and ablative methods (cryotherapy, excision, trichloroacetic acid and electrocautery). No treatment is also an option because approximately one-third of visible warts disappear spontaneously within 6 months.

Green tea leaf extract 10% ointment is listed in the BASHH guideline but is not included in the treatment algorithms. The guideline notes that the evidence to direct first- and second-line treatment is not strong and treatments have significant failure and relapse rates.

Full text of introduction and current guidance.

Product overview

Catephen 10% ointment contains *Camellia sinensis* (green tea) leaf extract. Its mechanism of action is not known (Catephen summary of product characteristics).

Catephen is licensed for the cutaneous treatment of external genital and perianal warts in immunocompetent adults. It is applied 3 times daily until all warts have cleared, or for a maximum duration of 16 weeks.

Catephen is available in a 15 g tube, costing £39.00 (MIMS, November 2015).

Full text of product overview.

Evidence review

This evidence summary is based on 2 randomised controlled trials (RCTs, Stockfleth et al. 2008 and Tatti et al. 2008) that compared green tea leaf extract 10% ointment with vehicle (placebo) for the treatment of external genital and perianal warts in adults for up to 16 weeks. The results of these 2 RCTs have been combined in a meta-analysis by Tatti et al. (2010). The pooled results are shown below.

- In 2 RCTs (total n=1005), green tea leaf extract 10% ointment (n=401) was more effective than vehicle ointment (n=207) for complete clearance of all baseline and newly developed genital and perianal warts (53.6% compared with 35.4% respectively, odds ratio 2.10, 95% confidence interval [CI] 1.49 to 2.98, p<0.001). Similar results were observed for the clearance of baseline warts only (excluding new warts that developed during the treatment period).
- Statistically significant differences between green tea leaf extract 10% and vehicle were observed for clearance of all warts at week 6, and for the rest of the 16-week treatment period.
- Participants with complete clearance of all warts during the treatment period entered into a 12-week follow-up phase to assess for recurrence. There was no statistically significant difference in recurrence rates for people receiving green tea leaf extract 10% (6.5%) compared with vehicle (5.8%). Recurrence rates beyond 12 weeks are not known.
- Treatment-emergent local skin reactions occurred in 82.9% of people receiving green tea leaf extract 10% and 60.4% of people receiving vehicle (statistical analysis not reported). Local skin reactions were mainly mild or moderate, and their frequency was independent on wart location.
- More people in the green tea leaf extract 10% group experienced severe local reactions compared with vehicle (27.4% and 4.4% respectively). Severe local reactions were more common in women than men (34.4% and 21.2% respectively). Few people discontinued treatment due to adverse effects (1.0% green tea extract and 0.5% vehicle).
- The maximum incidence of local reactions with active treatment was reached after 4 weeks. Tatti et al. (2010) suggest that local reactions at the application site are part of the mechanism of action for green tea leaf extract and necessary for achieving clinical response.
- Very common adverse events (occurring in at least 1 in 10 people) reported in the summary of product characteristics are erythema, pruritus, irritation or burning, pain, ulcer, oedema, induration (hardening of soft tissue) and vesicles.

Full text of evidence review.

Context

Green tea leaf extract 10% ointment is a new self-administered topical treatment for external genital and perianal warts. Other self-administered topical treatments available in the UK are podophyllotoxin 0.5% solution, podophyllotoxin 0.15% cream and imiquimod 5% cream.

The cost of topical treatments for genital and perianal warts depends on the unit cost of the medication, the area being treated and the duration of treatment. Based on the maximum dose and assuming the full treatment course is required, green tea leaf extract 10% ointment is the most costly topical treatment for external genital and perianal warts, at £234.00 for 16 weeks' treatment. Imiquimod 5% cream (Aldara) costs £194.40 for a 16 week course, and podophyllotoxin products (Warticon Cream, Warticon Solution and Condyline solution) cost between £14.49 and £17.83 for a 4 to 5 week course (prices from Drug Tariff, November 2015 or MIMS, November 2015).

Full text of context.

Estimated impact for the NHS

Prescribers and local decision makers need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using green tea leaf extract 10% ointment or another topical treatment for external genital warts. There are no RCTs comparing green tea leaf extract 10% ointment with other active treatments for external genital and perianal warts, and topical treatments have significant failure and relapse rates.

Full text of estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

Full evidence summary

Introduction and current guidance

Anogenital warts (*condylomata acuminata*) are benign, proliferative growths occurring in the genital, perineal, anal, and perianal areas. As well as occurring externally, lesions can also occur in the urethral orifice, vagina, cervix and anal canal. Anogenital warts are caused by human papillomavirus (HPV), most commonly 'low-risk' genotypes 6 and 11. However, there may be simultaneous infection with 'high-risk' HPV genotypes that are associated with anogenital cancer (NICE clinical knowledge summaries: warts – anogenital).

Public Health England reports that, in 2014, the total number of new cases of genital warts was 70,612, a 4% decrease since 2013 (Sexually transmitted infections and chlamydia screening in England: 2014). However, genital warts remain 1 of the most common conditions treated in genitourinary medicine clinics, with over 130,000 cases treated each year in the UK (UK national guidelines on the management of anogenital warts).

Genital warts appear from 3 weeks to 8 months after primary infection, most commonly developing after 2 to 3 months (The green book, chapter 18a). The majority of anogenital warts result in little physical discomfort, but may present with inflammation, fissuring, itching, bleeding, or dyspareunia (painful sexual intercourse; 2012 European guideline for the management of anogenital warts). Approximately one-third of visible warts disappear spontaneously within 6 months. However, most people seek treatment because of the discomfort, anxiety, distress or social unacceptability that warts cause (UK national guidelines on the management of anogenital warts).

The British Association for Sexual Health and HIV (BASHH) updated the UK national guidelines on the management of anogenital warts in 2015 (accredited by NICE). These recommend that treatment choice depends on the morphology, number and distribution of warts, and the person's preference. Treatment options include self-applied topical treatments (podophyllotoxin 0.5% solution or 0.15% cream, imiquimod 5% cream and green tea leaf extract 10% ointment), ablative methods (cryotherapy, excision, trichloroacetic acid and electrocautery) or no treatment. The guideline suggests that soft non-keratinised warts generally respond well to topical treatments, but keratinised lesions may be better treated with physical ablative methods.

BASHH note that the evidence to direct first- and second-line treatment is not strong and treatments have significant failure and relapse rates. Also, there is a lack of comparative clinical trial data on which to base recommendations on the preferred home-based and clinic-based treatments. Green tea (*Camellia sinensis*) leaf extract 10% ointment (Catephen), which is the subject of this evidence summary, is listed in the BASHH guideline but is not included in the treatment algorithms (UK national guidelines on the management of anogenital warts).

Treatments for anogenital warts focus on removal of the lesions, but do not necessarily eliminate infection, which may persist sub-clinically and be a source of recurrence and continuing viral transmission. The national HPV immunisation programme was introduced in September 2008, primarily to protect against cervical cancer. Gardasil is the vaccine that has been used in girls and young women since September 2012. In young women, it is reported to be 99% effective for preventing genital warts associated with the types of HPV covered by the vaccine (The green book, chapter 18a).

Product overview

Drug action

Catephen 10% ointment contains 100 mg of green tea (*Camellia sinensis*) leaf extract per 1 g of ointment. The mechanism of action of green tea leaf extract is not known. In non-clinical studies, the extract acts by inhibiting the growth of activated keratinocytes and by anti-oxidative effects at the site of application. The clinical significance of these findings is unknown (Catephen summary of product characteristics).

Licensed therapeutic indication

Catephen 10% ointment is licensed for the cutaneous treatment of external genital and perianal warts in immunocompetent adults. The summary of product characteristics for Catephen states that it should not be used for the treatment of internal (urethral, intra-vaginal, cervical, rectal or intra-anal) warts because it has not been evaluated in these conditions.

Green tea leaf extract 10% ointment is available in Germany under the brand name Veregen. The UK marketing authorisation for the product, with the brand name Catephen, was approved in March 2015 under the EU mutual recognition procedure. The public

assessment report referred to in this evidence summary is for Veregen.

Green tea (*Camellia sinensis*) leaf extract is referred to by several different names in the published literature, including 'sinecatechins' and 'Polyphenon E'.

Course and cost

According to the summary of product characteristics, Catephen 10% ointment should be applied 3 times daily, with treatment continued until there is complete clearance of all warts. The maximum duration of treatment is 16 weeks, even if new warts develop during the treatment period.

A small amount of Catephen 10% ointment should be applied to each wart, with up to 250 mg of ointment (approximately 0.5 cm of ointment strand) applied as total single dose (maximum daily dose 750 mg).

Catephen 10% ointment is for cutaneous use only and should not be applied to mucous membranes.

Catephen 10% ointment costs £39.00 per 15 g tube. Based on a maximum daily dose of 750 mg, a 15 g tube would provide approximately 20 days' treatment, with 6 tubes required for the maximum 16 week treatment course, costing £234.00 (MIMS, November 2015).

Evidence review

This evidence summary discusses 2 randomised controlled trials (RCTs, Stockfleth et al. 2008 and Tatti et al. 2008) that evaluated green tea leaf extract 10% ointment for the treatment of external genital and perianal warts in adults. Results of a meta-analysis of these 2 RCTs are also included (Tatti et al. 2010). The results of an earlier phase II/III supportive study that did not include the formulation of green tea leaf extract available in the UK are not discussed (Gross et al. 2007).

Stockfleth et al. 2008 and Tatti et al. 2008

- Design: Both studies were randomised, double-blind, vehicle-controlled trials.

- Population: The study by Stockfleth et al. (2008) was conducted in Europe and South Africa (n= 503) and the study by Tatti et al. (2008) was undertaken in the USA, Latin America and Romania (n= 502). Both studies recruited men and women aged 18 years or older (mean age 31 years) with 2 to 30 external genital and perianal warts (mean number at baseline 8 warts, Tatti et al. 2010) and a total wart area of 12 mm^2 to 600 mm^2 (mean area at baseline approximately 95 mm^2, Tatti et al. 2010). In Stockfleth et al. (2008), all participants had previous episodes of genital warts; in Tatti et al. (2008) the majority of participants (82.5%, 414/502) did not have previous episodes. The mean time between the start of the current episode and the start of study treatment was 31.5 weeks in Stockfleth et al. (2008) and approximately 49 weeks in Tatti et al. (2008). Baseline characteristics were reported to be similar between the groups in both studies.

- Intervention: In both trials, participants were randomised 2:2:1 to green tea leaf extract 15% ointment, 10% ointment and vehicle (placebo). It is unclear if allocation was concealed. The 15% preparation is not available in the UK and the results for this strength are not discussed in detail in this evidence summary. Participants applied the ointment 3 times a day to all external genital warts. The medium dosage used across the 2 studies was 456.1 mg/day (range 23.8 mg to 1283 mg, public assessment report). The maximum duration of treatment was 16 weeks, or until complete clearance of all (baseline and new) warts. No additional topical treatments were allowed and oral paracetamol was permitted for the treatment of local skin reactions.

- Efficacy outcomes: The primary efficacy end point in both studies was complete clearance of warts that were present at baseline or developed during the study. Secondary efficacy end points included complete clearance of baseline warts, total wart number, total wart area, partial clearance (area), time to clearance and new warts during treatment. Participants with complete clearance were entered into a 12 week treatment-free follow-up phase to assess for recurrence of warts.

- Safety outcomes: Local skin reactions were reported separately from other adverse events. Investigators assessed local skin signs including erythema, oedema, induration, vesicles and erosion or ulceration. Participants were asked about local skin symptoms, including burning, itching and pain.

- Analysis: In both studies, efficacy analyses were performed on the modified intention-to-treat (mITT) population, which included all participants with a baseline and at least 1 other efficacy assessment. The safety population included all randomised participants who received at least 1 application of study medication.

Table 1 Summary of Stockfleth et al. 2008

	Green tea leaf extract 10% ointment	Vehicle	Analysis
Randomised	n=199	n=103	
Efficacy[a]	n=195	n=102	
Primary outcome: complete clearance of all warts (baseline and new)	50.8% (99/195)	37.3% (38/102)	Statistically significant difference, p=0.0280
Selected secondary outcomes:			
Median time to complete clearance of all warts	16.4 weeks	16.7 weeks	No statistically significant difference between groups
Complete clearance of baseline warts	52.3% (102/195)	39.2% (40/102)	Statistically significant difference, p=0.0376
Median total number of warts	Baseline 6 End of treatment 0	Baseline 6 End of treatment 3	Statistically significant difference, p=0.0025
Safety[b]	n=198	n=103	
Participants reporting local skin reactions during treatment	81.5% (159/195)[c]	61.8% (63/102)[c]	No statistical analysis reported
Participants with investigator reported severe local skin signs	4.0% (8/198)	1.9% (2/103)	No statistical analysis reported
Participants reporting adverse events other than local reactions	23.7% (47/198)	21.4% (22/103)	No statistical analysis reported

Participants reporting adverse events other than local reactions that were considered possibly related to study medication	1.5% (3/198)	1.9% (2/103)	No statistical analysis reported

Abbreviations: p, p value

[a] Modified intention-to-treat (mITT) population: all participants with a baseline and at least 1 other efficacy assessment

[b] Safety population: all randomised participants who received at least 1 application of study medication

[c] The percentage of participants reporting local skin reactions appear to relate to the efficacy population, rather than the safety population described.

Table 2 Summary of Tatti et al. 2008

	Green tea leaf extract 10% ointment	**Vehicle**	**Analysis**
Randomised	n=202	n=104	
Efficacy[a]	n=197	n=104	
Primary outcome: complete clearance of all warts	56.3% (111/197)	33.7% (35/104)	Statistically significant difference, p<0.001
Selected secondary outcomes:			
Complete clearance of baseline warts	60.9% (120/197)	33.7% (35/104)	Statistically significant difference, p<0.001
Median total number of warts	Baseline 6 End of treatment 0	Baseline 7 End of treatment 2.5	Statistically significant difference, p<0.014

Safety[b]	n=202	n=104	
Participants reporting local skin reactions during treatment	87.3% (172/202)[c]	72.1% (75/104)[c]	No statistical analysis reported
Participants reporting adverse events other than local reactions that were considered to be possibly related to study medication	7.4% (15/202)	Not reported	

Abbreviations: p, p value

[a] Modified intention-to-treat (mITT) population: all participants with a baseline and at least 1 other efficacy assessment

[b] Safety population: all randomised participants who received at least 1 application of study medication

[c] The percentage of participants reporting local skin reactions appear to relate to the efficacy population, rather than the safety population described.

Clinical effectiveness

Clearance of baseline and new warts

In 2 RCTs (Stockfleth et al. 2008 and Tatti et al. 2008), statistically significantly more people treated with green tea leaf extract 10% ointment experienced complete clearance of all (present at baseline or developed during treatment) external genital and perianal warts compared with vehicle. Pooled results of the 2 RCTs (n=1005) found 53.6% of people receiving green tea leaf extract 10% ointment (n=401) and 35.4% of people receiving vehicle (n=207) experienced complete clearance of all warts after a maximum of 16 weeks' treatment (odds ratio [OR] 2.10, 95% confidence interval [CI] 1.49 to 2.98, p<0.001; Tatti et al. 2010). Statistically significant differences between green tea leaf extract 10% and vehicle were observed for this outcome at week 6, and for the rest of the 16-week treatment period (Tatti et al. 2010). The median time to clearance of all warts was 16.4 weeks for green tea leaf extract 10% and 16.9 weeks for vehicle, although it is not clear how this was determined (public assessment report, no statistical analysis reported).

Rates of complete clearance of all warts were higher in women than men (62.8% compared with 45.5% for green tea leaf extract 10%). It has been suggested that this

difference in efficacy may be because men experience more skin keratinisation, which may inhibit drug absorption (Tatti et al. 2010).

Clearance of baseline warts

Similar results were observed for the clearance of baseline warts (excluding any new warts that developed during treatment), with statistically significant improvements with green tea leaf extract 10% ointment compared with vehicle in both studies (Stockfleth et al. 2008 and Tatti et al. 2008; see tables 1 and 2 for results).

At the end of the treatment period, an increase in total wart area from baseline was observed in less than 10% of people who used green tea leaf extract (10% or 15%), compared with 16.1% who used vehicle (no statistical analysis reported, Tatti et al. 2010).

New warts during treatment

The public assessment report states that the development of new warts during the treatment phase was relatively common in both studies, occurring in about 40% of participants in the green tea leaf extract 10% ointment and placebo groups. The rate of clearance of all new warts was 58.5% in the active treatment group compared with 42.4% in the vehicle group (no statistical analysis reported).

Recurrence of warts

There was no statistically significant difference in recurrence rates during the 12 week follow-up period for people receiving green tea leaf extract 10% (6.5%, 13/201) compared with vehicle (5.8%, 4/69; p value not reported). Few participants developed new warts during follow-up, with no statistically significant difference between the treatment groups (Tatti et al. 2010).

Green tea leaf extract 15% ointment

Similar efficacy results were seen with green tea leaf extract 15% ointment (not available in the UK), with 54.9% (213/388) of participants achieving complete clearance of all warts compared with 53.6% (210/392) of people receiving the 10% ointment (Tatti et al. 2010). The public assessment report states that the difference between the 15% and 10% strengths was not considered clinically important. In addition, the 10% strength had a better safety profile than the 15% strength.

Safety and tolerability

The number of adverse events related to the study treatment other than local reactions at the administration site was low. By comparison, the incidence of treatment-emergent local skin reactions was high across both studies, occurring in 82.9% (324/400) of people receiving green tea leaf extract 10% and 60.4% (125/207) of people receiving vehicle (statistical analysis not reported). The maximum incidence of local reactions was reached after 4 weeks' treatment with the 10% ointment (Tatti et al. 2010). Local skin reactions were mainly mild or moderate, and their frequency was independent on wart location (public assessment report).

The number of people with 1 or more severe local reactions was higher in the green tea leaf extract 10% group (27.4%, 107/400) compared with the vehicle group (4.4%, 9/207). The incidence of any local reaction was similar for men and women receiving the active treatment (81.7% and 84.2% respectively), although more women experienced severe local reactions (34.4% compared with 21.2%; statistical analysis not reported for these outcomes, Tatti et al. 2010). It has been suggested that local reactions at the application site are part of the treatment's mechanism of action and are necessary for achieving clinical response (Tatti et al. 2010).

Discontinuation rates from the studies due to adverse events were generally low, with 4 people in the green tea leaf extract 10% group and 1 person in the vehicle group withdrawing for this reason (Tatti et al. 2010).

Analysis showed that complete clearance of all warts was statistically significantly associated with erosion or ulceration (OR 1.87, 95% CI 1.36 to 2.57) and erythema (OR 1.61, 95% CI 1.16 to 2.24).

The summary of product characteristics for green tea leaf extract 10% ointment states that local reactions at the application site (erythema, pruritus, irritation or burning, pain, ulcer, oedema, induration [hardening of soft tissue] and vesicles) are very common, occurring in at least 1 in 10 people. Local reactions such as exfoliation, discharge, bleeding and swelling occur in between 1 in 100 and 10 in 100 people receiving the 10% ointment. Other common reactions reported in the summary of product characteristics are inguinal lymphadenitis or lymphadenopathy and phimosis.

Green tea leaf extract 15% is not available in the UK because it is associated with a higher incidence of adverse events compared with the 10% strength, with no efficacy benefits.

Across the 2 RCTs, the incidence of moderate and severe local skin reactions was higher in the green tea leaf extract 15% group compared with the 10% group (65.3% and 59.7% respectively (public assessment report). The public assessment report concluded that green tea leaf extract 10% had a superior safety profile compared with the 15% strength.

The 2012 European guideline for the management of anogenital warts states that up to 65% of people treated with podophyllotoxin experience transient burning, tenderness, erythema and erosions. The summary of product characteristics for imiquimod reports that application site reactions occur in approximately 33.7% of people treated with imiquimod. Indirect comparisons must be interpreted with caution due to differences in study methodologies and populations.

Evidence strengths and limitations

Green tea leaf extract 10% ointment has not been directly compared to other active treatments for the management of external genital and perianal warts, making it difficult to assess its relative safety and efficacy, and appropriate place in therapy. However, it should be noted that there is currently a lack of comparative trial data for all self-administered topical treatments for external genital and perianal warts (UK national guidelines on the management of anogenital warts).

Clearance rates for other topical treatment for genital warts are summarised in the 2012 European guideline for the management of anogenital warts. Podophyllotoxin 0.5% solution achieved clearance rates of between 45% and 83% after 3 to 6 weeks' treatment. Similar results have been seen with podophyllotoxin 0.15% cream (43% to 70% clearance rates reported at 4 weeks). Clearance rates of between 35% and 68% after 16 weeks' treatment have been reported for imiquimod 5% cream. For comparison, the European guidelines report clearance rates of 47% to 59% for green tea leaf extract 10% and 15% ointments following 12 to 16 weeks' treatment. Such indirect comparisons must be interpreted with caution due to differences in study methodologies and populations.

In Stockfleth et al. (2008) and Tatti et al. (2008), approximately 35% of people who received vehicle experienced complete clearance of all warts. This is slightly higher than the spontaneous cure rate of about 28% reported in the literature for other dermatological treatments, although rates of spontaneous regression in other trials vary considerably (public assessment report).

All participants who had complete clearance of all warts during the treatment phase were

entered into a 12-week follow-up period to assess recurrence. Recurrence rates were low for both green tea leaf extract 10% and vehicle (6.5% and 5.8% respectively) with no statistically significant difference between the groups (Tatti et al. 2010). However, the latency for HPV infection is long, meaning the 12 week follow-up period may not have been sufficient to detect the long-term effect of treatment. A 6-month follow-up period may have provided better information on longer term recurrence rates (Tatti et al. 2010). Recurrence rates reported in trials of other topical treatments are higher, ranging from 6% to 100% (2012 European guideline for the management of anogenital warts). However, some trials have reported recurrence rates for up to 6 months after treatment and several trials experienced high loss to follow-up. In addition, indirect comparisons of different trials should be considered with caution (2012 European guideline for the management of anogenital warts).

The maximum duration of treatment for green tea leaf extract 10% in clinical trials was 16 weeks and the efficacy and safety profile beyond this time period is not known. Therefore, the product is licensed for up to 16 weeks only.

Context

Costs of alternative self-applied topical treatments

Drug	Usual adult dose[a]	Cost of maximum treatment length excluding VAT
Green tea (*Camellia sinensis*) leaf extract 10% ointment (Catephen)	Apply up to 250 mg (0.5 cm) 3 times daily. Maximum duration of treatment 16 weeks	£234.00[b]
Imiquimod 5% cream (Aldara)	Apply 3 times a week at night, for a maximum of 16 weeks	£194.40[c]
Podophyllotoxin 0.5% solution (Condyline)	Apply twice daily for 3 days. If necessary, repeat at weekly intervals for 5 weeks	£14.49[b]
Podophyllotoxin 0.5% solution (Warticon Solution)	Apply twice daily for 3 days. If necessary, repeat at weekly intervals for 4 weeks	£14.86[b]

Podophyllotoxin cream 0.15% (Warticon Cream)	Apply twice daily for 3 days. if necessary, repeat at weekly intervals for 4 weeks	£17.83[c]

[a] Doses shown do not represent the full range that can be used and do not imply therapeutic equivalence. Taken from the relevant summaries of product characteristics unless stated otherwise.

[b] Costs based on MIMS, November 2015; excluding VAT.

[c] Costs based on the Drug Tariff, November 2015; excluding VAT.

Estimated impact for the NHS

Likely place in therapy

Green tea leaf extract 10% ointment is a self-administered topical treatment for external genital and perianal warts. There are limited options for people requiring self-administered topical treatments for anogenital warts, and no comparative data to facilitate choosing between them.

The UK national guidelines on the management of anogenital warts highlight that the evidence base to direct first- and second-line treatments is not strong and treatments have significant failure and relapse rates. Also, approximately one-third of visible warts disappear spontaneously within 6 months, so no treatment is an option. The guidelines emphasise the need for person-centred care, with treatment decisions made only after discussing the appropriate options with the patient, taking into account their preference.

Clearance of all external genital and perianal warts was found to be 2-fold higher with green tea leaf extract 10% ointment than with vehicle over 16 weeks, with a statistically significant difference between the groups seen from 6 weeks. Although local skin reactions were common, green tea leaf extract was generally well tolerated, with few serious adverse events or discontinuations.

Although cost is dependent on the area of the warts and the length of treatment, green tea leaf extract 10% ointment is more expensive over the maximum licensed treatment duration than other self-administered topical treatments (£234.00 compared with £194.40 for imiquimod and between £14.49 and £17.83 for podophyllotoxin). However, it is difficult to make direct comparisons, particularly as treatment efficacy and recurrence rates need

to be taken into account.

Green tea leaf extract, podophyllotoxin and imiquimod are available in a variety of formulations and may vary in their ease of application. They have differing dosing schedules and maximum treatment periods, which may also affect a person's choice. Applying a treatment 3 times daily might be difficult for some people.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using green tea leaf extract 10% ointment or another topical treatment for external genital warts.

Estimated usage

The manufacturer of Catephen estimates that in the first year after launch approximately 978 people will be treated with green tea leaf extract 10%, increasing to approximately 4888 people after 5 years (personal communication Kora Healthcare).

Relevance to NICE guidance programmes

Green tea leaf extract is not considered appropriate for a NICE technology appraisal and is not currently planned into any other NICE work programme.

NICE has issued public health guidance on the prevention of sexually transmitted infections and under-18 conceptions.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Dr Gilson has non-personal, specific interests in 2 other products that are used to treat the same condition in that he is the chief investigator of a trial funded by the NIHR-HTA programme which includes a comparison of imiquimod and podophyllotoxin treatment for the same indication. Dr Gilson is lead author of the British Association for Sexual Health and HIV Association national guidelines on the management of anogenital warts.

Dr Lawton has received speakers fees and honoraria for advisory boards from Gilead Sciences Ltd, Merck Sharp & Dohme, Viiv Healthcare and Janssen Therapeutics.

Dr Kell has no interests to declare.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

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