Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND
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camellia sinensis (green tea) leaf extract 10% ointment (Catephen®)

SMC No. (1133/16)

Kora Healthcare

04 March 2016

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

camellia sinensis (green tea) leaf extract (Catephen®) is accepted for restricted use within NHS Scotland.

Indication under review: Cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years.

SMC restriction: for use in patients not suitable for podophyllotoxin or who have not responded to treatment with podophyllotoxin.

Complete clearance of baseline and new warts was achieved in a significantly higher proportion of patients treated for up to 16 weeks with camellia sinensis (green tea) 10% ointment than vehicle ointment, in two phase III randomised double-blind studies.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Cutaneous treatment of external genital and perianal warts (*condylomata acuminata*) in immunocompetent patients from the age of 18 years.

Dosing Information

Apply up to 250mg camellia sinensis (green tea) ointment as total single dose, corresponding to about 0.5cm of ointment strand three times per day to all external genital and perianal warts (750mg total daily dose).

Treatment with camellia sinensis (green tea) ointment should be continued until complete clearance of all warts, however, no longer than 16 weeks in total (maximum duration), even if new warts develop during the treatment period.

Product availability date

15 September 2015.

Summary of evidence on comparative efficacy

Anogenital warts are caused by human papillomavirus (HPV) of which there are over 100 genotypes, although about 90% of cases are caused by HPV-6 and HPV-11. The annual incidence of genital warts in developed world populations has been estimated to be around 0.15% of the adult population per year. In the UK, genitourinary medicine (GUM) clinics treat over 130,000 cases of genital warts annually but numbers are expected to decline due to the availability of the HPV vaccine (effective against HPV-6 and HPV-11) which is offered in Scotland to girls aged 11 to 13 years. [1, 2]

The exact mechanism of action of camellia sinensis (green tea) is not known. In non-clinical studies, the extract from green tea leaves 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. [3]

The submitting company has requested that SMC considers camellia sinensis when positioned for use in patients not suitable for podophyllotoxin or who have not responded to treatment with podophyllotoxin.

Two similar, phase III, randomised, double-blind, vehicle-controlled studies (CT1017 and CT1018) have been conducted in adult patients with 2 to 30 external genital and perianal warts and a total wart area of 12 to 600mm^2. Patients were randomised in a ratio of 2:2:1 to topical treatment with camellia sinensis (green tea) 10% ointment (licensed product), camellia sinensis (green tea) 15% ointment or vehicle ointment. The ointment was applied three times daily (with around eight hours between each application) to all external genital and perianal warts. Oral paracetamol was permitted for local skin reactions. No other topical treatments were permitted. Patients were treated until week 16 or until they had completed clearance of all warts. Those with complete clearance were followed up for a further 12 weeks to assess recurrence rates.[4,5]

The primary outcome was the proportion of patients with complete clearance of all (baseline and new) warts within the 16-week treatment period. This was conducted in the intent-to-treat (ITT) population which included patients with baseline and at least one post-baseline efficacy assessment and used last observation carried forward (LOCF). Study CT1017 randomised 503 patients; all patients had a previous episode of external genital and perianal warts and 36% had received previous treatment. Study CT1018 recruited 502 patients and 18% had a previous episode of external genital and perianal warts. Recurrence rate was a secondary endpoint. [4,5]

The proportion of patients with complete clearance was significantly higher for patients treated with camellia sinensis (green tea) 10% than vehicle. In the camellia sinensis (green tea) 10% and vehicle groups respectively, a higher proportion of women (63% and 44%) than men (46% and 29%) achieved complete clearance. Results of the primary endpoint and secondary endpoint of recurrence are presented in table 1 for the camellia sinensis (green tea) 10% and vehicle groups in the individual studies and the pooled analysis. [4-6]

Table 1: Complete response and recurrence rates for studies and pooled analysis in the ITT efficacy analysable population[4-6]

	Study CT1017		**Study CT1018**		**Pooled analysis**	
	camellia sinensis (green tea) 10%	vehicle	camellia sinensis (green tea) 10%	vehicle	camellia sinensis (green tea) 10%	vehicle
n (ITT)	n=195	n=102	n=197	n=104	n=392	n=206
Primary endpoint						
Complete response, % (n/N)	51% (99/195)	37% (38/102)	56% (111/197)	34% (35/104)	54% (210/392)	35% (73/206)
p-value	p=0.0281		p<0.001		p<0.001 odds ratio 2.10 (95% CI: 1.48 to 2.98)	
Secondary endpoint						
Recurrence rate % (n/N)	4.0% (4/99)	2.6% (1/38)	8.3%	8.8%	6.5% (13/201)	5.8% (4/69)

ITT=intention to treat; CI=confidence interval

Complete clearance of baseline warts was also significantly higher for camellia sinensis (green tea) 10% than vehicle: 52% versus 39% (in study CT1017) and 61% versus 34% (in study CT1018).[4,5] In the pooled analysis, the proportion of patients with partial (50%) clearance of warts at week 16 was 76% for camellia sinensis (green tea) 10% and 52% for the vehicle group.[6]

Summary of evidence on comparative safety

In the pooled analysis, adverse events occurred in 32% (131/400) of patients in the camellia sinensis (green tea) 10% group and 28% (58/207) in the vehicle group. Adverse events considered related to study treatment occurred in 7.0% (28/400) and 2.4% (5/207) of patients respectively and very few were classed as serious. One patient in the camellia sinensis (green tea) 10% group developed pustular vulvovaginitis. Four patients in the camellia sinensis (green

tea) 10% group and one patient in the vehicle group discontinued from the study due to treatment-emergent adverse events. [6]

Treatment-emergent local reactions (signs and symptoms) which were pro-actively assessed by the investigator during the study occurred in 83% (324/400) of camellia sinensis (green tea) 10% treated patients and 60% (125/207) of patients in the vehicle group, and were similar for males and females. The maximum incidence occurred at week 4 for the camellia sinensis (green tea) 10% group and then declined gradually until the end of treatment. The proportion of patients with at least one severe local reaction was 27% (107/400) versus 4.4% (9/207) in the camellia sinensis (green tea) 10% and vehicle groups respectively. The proportion of patients with at least one severe local reaction was higher for females (34% versus 10%) than males (21% versus none) in the camellia sinensis (green tea) 10% and vehicle groups respectively. Severe local symptoms (reported by patients) occurred more frequently than severe local signs (objectively assessed by investigators) in all groups.[6]

It has been postulated that local skin reactions such as erythema, oedema and itching occur following stimulation (by camellia sinensis [green tea]) of the immune system locally, releasing proinflammatory cytokines. An analysis using logistic regression showed that complete clearance of all warts was significantly associated with erosion/ulceration (odds ratio 1.87, 95% CI: 1.36 to 2.57) and erythema (odds ratio 1.61, 95% CI: 1.16 to 2.24). The summary of product characteristics notes that these local skin reactions are very common, should not lead to discontinuation and should decrease after the first weeks of treatment.[3,4,6]

Summary of clinical effectiveness issues

Camellia sinensis (green tea) 10% ointment is licensed for the treatment of external genital and perianal warts in immunocompetent patients from the age of 18 years.[3] Other self-administered topical treatments include podophyllotoxin (0.15% cream, 0.5% topical solution), which may be used first-line, and imiquimod 5% cream, used if there is insufficient response to podophyllotoxin. As around 30% of patients will experience spontaneous clearance of warts over a period of up to six months, 'no treatment' may also be considered as a treatment approach.[1] Clinical experts consulted by SMC considered there is unmet need in this therapeutic area in terms of availability of highly effective treatments which are tolerated. In addition they noted that licensed treatments for adolescents and perianal warts are limited.

Complete clearance of baseline and new warts was achieved in a significantly higher proportion of patients treated with camellia sinensis (green tea) 10% ointment than vehicle ointment in two phase III randomised double-blind studies. One study was conducted in patients with previous genital wart episode(s) and in the other study the majority of patients had no previous episodes. Complete clearance rates were higher in women than men in both groups. The authors of the pooled analysis publication suggested that this may be explained by reduced ointment diffusion in men due to greater skin keratinisation. UK guidance notes that keratinised warts may respond better to physical ablative methods.[1,4-6]

The clearance rate in the vehicle groups for both studies was generally considered to be higher than in other studies of self-administered treatments. This may be explained by the activity of the vehicle itself as well as increased hygiene, and frequent mechanical interaction (due to thrice daily administration) which may have contributed to the healing.[6]

In the studies, the mean time from the start of the current episode to study entry was 58 weeks for the camellia sinensis (green tea) 10% group and 77 weeks for the vehicle group. [6] This is longer than six months, the period in which spontaneous clearance of warts is expected to occur (for around 30% of patients).[1] Therefore, the study population is likely to be considered eligible for treatment in clinical practice.

Following NDC, the submitting company clarified that SMC should consider camellia sinensis when positioned for use in patients not suitable for podophyllotoxin or who have not responded to treatment with podophyllotoxin. Therefore, they consider that imiquimod would be the relevant comparator. In pooled analysis of studies CT1017 and CT1018, 33% of patients in the camellia sinensis (green tea) 10% group and 38% in the vehicle group had a history of previous treatment and the proportion treated with podophyllotoxin is small. [6] Therefore, there are limited data for use of camellia sinensis (green tea) ointment after podophyllotoxin. As podophyllotoxin preparations are licensed for genital warts only,[7-10] licensed topical self administered treatments for perianal warts are limited to camellia sinensis (green tea) or imiquimod.

There are no direct comparative efficacy and safety data versus the other topical treatments that are self-administered. The submitting company reported results of a systematic literature review and naive indirect comparison of treatments licensed in Germany for external genital and perianal warts.[11] Naive indirect comparisons have severe limitations and do not provide robust indirect comparative data. Therefore, no conclusions can be drawn in terms of relative effectiveness of camellia sinensis (green tea) 10% ointment and the topical treatment comparators. An adjusted/anchored indirect comparison or network meta-analysis was requested and the submitting company provided a Bucher indirect comparison. This included three studies of Camellia sinensis (green tea) 10% ointment and five studies of imiquimod 5%. Two endpoints were reported: complete clearance and recurrence. There were limitations with the indirect comparison including heterogeneity between the studies and variation in the results of endpoints for the placebo arms of the camellia sinensis and imiquimod studies. These issues mean that limited conclusions can be made.

The administration schedules and licensed indications of topical treatments vary. Camellia sinensis (green tea) 10% ointment is applied three times per day and continued until complete clearance of all warts, up to a maximum duration of 16 weeks. Imiquimod 5% cream is applied three times per week, with the cream remaining on the skin for 6 to 10 hours; the maximum treatment duration is 16 weeks.[3,7]

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing camellia sinensis (green tea) 10% to imiquimod 5% cream for the treatment of external genital and perianal warts in immunocompetent patients from the age of 18 years, when podophyllotoxin is not suitable or patients have not responded to treatment. SMC clinical expert responses indicate that imiquimod is the appropriate comparator.

The economic model incorporates costs and quality adjusted life-years (QALYs) associated with each treatment over two treatment cycles i.e. the same topical treatment is repeated if there is recurrence or non-clearance after the initial treatment. If warts remain after the second treatment cycle, these are removed by surgery.

The clinical data used in the economic model were taken from the results of a naive indirect comparison, where the primary outcomes were clearance and recurrence rates of genital warts. Based on this analysis, camellia sinensis (green tea) 10% was estimated to have a clearance rate of 54.4% and a recurrence rate of 7.7%, and imiquimod 5% cream was associated with a clearance rate and a recurrence rate of 43.1% and 18.2% respectively.

The base case analysis was based on medicine costs only; however, an additional analysis incorporating GP/GUM costs, as well as the cost of surgical removal for remaining warts that had not cleared or had recurred after topical treatment, was also provided. Adverse event costs associated with treatment were not included in the analysis.

Quality of life loss due to an episode of genital warts (estimated to be 6.6 days) was derived from a published study of patients presenting to clinics in England and Northern Ireland using the EQ-5D. In order to calculate the total quality adjusted days lost following the initial dose, repeat dose and surgical removal, treatment specific clearance and recurrence rates were applied.

Camellia sinensis (green tea) 10% resulted in an incremental cost effectiveness ratio (ICER) of £4,398 compared to imiquimod 5% cream, based on an incremental cost of £40 (difference in drug costs only) and an incremental QALY gain of 0.009. The QALY gain associated with camellia sinensis stemmed from fewer episodes, as camellia sinensis was assumed to have a higher clearance rate and lower recurrence rate compared to imiquimod. When the analysis incorporated differences in clearance and recurrence rates plus GP/GUM visit costs and surgical removal costs associated with each treatment, camellia sinensis was the dominant treatment with overall savings of £234 compared to imiquimod.

Limited sensitivity analysis has been provided; however, the company has tested certain key parameters e.g. varying the clearance and recurrence rates, and using values from a single published study. When the lowest clearance rate and highest recurrence rate for both camellia sinensis and imiquimod were used, camellia sinensis resulted in savings of £323 versus imiquimod. When the highest clearance rates and lowest recurrence rate for both camellia sinensis and imiquimod were used, camellia sinensis resulted in savings of £156 versus imiquimod. When recurrence rates for both treatments were assumed to be equivalent i.e. 7.7%, the ICER increased to £9,998 based on an incremental cost of £40 and an incremental QALY gain of 0.00396.

The limitations with the analysis are as follows:

- There are a number of concerns surrounding the clinical data used within the economic analysis. There is a lack of data comparing camellia sinensis to imiquimod and limited evidence available in the relevant patient group as the pivotal studies did not specifically recruit patients who had received previous treatments. The pooled analysis reported that only 16% of patients in the camellia sinensis arm and 10% of patients in the vehicle group had received previous treatment with podophyllotoxin. As such, the available clinical data used in the economic analysis is limited.
- Statistical evidence to support the differences between treatments in terms of clearance and recurrence rates (which were derived from the naïve indirect comparison) was not initially provided. As such, there is considerable uncertainty surrounding the validity of the treatment effect associated with camellia sinensis. In addition, as the QALY gain is derived via the application of clearance and recurrence rates, there is further concern surrounding the validity of the QALY gain. In order to address some of the clinical uncertainty i.e. lack of comparative data and statistical results, the company was asked to provide an adjusted

anchored indirect comparison. This was subsequently provided, but due to the heterogeneity and variation within the included studies, the validity of the clearance and recurrence rates used within the analysis remains unclear.

Despite the weaknesses outlined above, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Group submission was not made.

Additional information: guidelines and protocols

The British Association for Sexual Health and HIV (BASHH) UK National Guidelines on the Management of Anogenital Warts were available online in 2015.[1] Treatment choice depends on the morphology, number, and distribution of warts and patient preference. The guidelines note that the evidence base to direct first and second line treatments is not strong and that all treatments have significant failure and relapse rates. Around 30% of patients will experience spontaneous clearance of warts over a period of up to six months therefore no treatment may also be an option. However most patients seek treatment for the discomfort, anxiety, distress or the social unacceptability that warts cause. The guideline notes that soft non-keratinised warts respond well to podophyllotoxin, and trichloroacetic acid, while keratinised warts may respond better to physical ablative methods (ie cryotherapy, excision, trichloroacetic acid or electrocautery. Imiquimod is suitable treatment for both keratinised and non-keratinised warts. The guidelines detail separate treatment algorithms for women and for men.

- Men and women with multiple external genital or perianal warts should receive podophyllotoxin twice daily three days a week and then be reviewed after four to five weeks.
    - If more than 50% resolved, then treatment should be continued.
    - If less than 50% resolved imiquimod 5% cream once daily on alternate days for three days a week up to week 16 should be given.
    - If the warts have still not resolved, consideration should be given to repeating treatment or excision.
- For men and women with few warts or women who are pregnant, cryotherapy once weekly should be offered, with review after four weeks.
    - If more than 50% resolved, treatment should be continued.
    - If less than 50% resolved then switch to imiquimod or podophyllotoxin. Then if still not cleared consideration should be given to repeating treatment or excision.
    - In cases where pregnant women experience less than 50% resolution, then excision or delaying until after pregnancy should be considered.

The guidelines note that mechanism of action of camellia sinensis (green tea) 10% ointment is uncertain. They state that while there are no comparative data with other topical treatments, the study results are consistent with a similar effect and local reactions.

The 2012 European guideline for the management of anogenital warts was published in 2013.[12] Guidance for home- and clinic-based treatments is provided. Home-based treatments include podophyllotoxin 0.15% cream or 0.5% solution, imiquimod 5% cream and camellia sinensis (green tea) 10% ointment. Clinic-based treatments include cryotherapy, trichloroacetic acid and electrosurgery/scissors excision/curettage/laser. Treatment choices, which should be discussed between doctor and patient, are based on morphology and extent of warts. In patients with

limited disease (1 to 5 warts) clinic-based treatments may be preferred. No treatment is an option as warts may regress spontaneously in some patients.

The National Institute for Health and Care Excellence (NICE) published evidence summary (ES) ESNM66; external genital and perianal warts: green tea (camellia sinensis) leaf extract 10% ointment, in December 2015.[13] The evidence summary notes that no published comparisons with other active treatments for genital and perianal warts are available.

Additional information: comparators

Imiquimod 5% cream, or no treatment.[7]

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Camellia sinensis (green tea) 10% ointment	**Apply up to 250mg three times per day for up to 16 weeks.**	**up to 234**
Imiquimod 5% cream	Apply three times per week for up to 16 weeks.	up to 194

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 11 December 2015.

* Any residual warts should be treated with further courses at weekly intervals for up to five weeks (Condyline®) of treatment; costs for four courses are provided.

Additional information: budget impact

The submitting company estimated there to be 15,008 patients eligible for treatment in year 1 and 11,339 in year 5, with an estimated uptake rate of 4% in year 1 and 15% in year 5.

The gross medicines budget impact was estimated to be £148k in year 1, rising to £399k in year 5. As other medicines were assumed to be displaced, the net budget impact decreased to £65k in year one and £86k in year 5.

References

The undernoted references were supplied with the submission.

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4. Stockfleth E, Beti H, Orasan R, Grigorian F, Mescheder A, Tawfik H, et al. Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. British Journal of Dermatology. 2008;158(6):1329-38.
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11. Schafer T, Schnoor M. Data analysis for clearance and recurrence rates; self-treatment of condylomata acuminate with medication [translation from German]. Der Deutsche Dermatologe. 2014;62:200-7.
12. Lacey C WS, Wikstrom A et al,. 2012 European guideline for the management of anogenital warts. Journal of the European Academy of Dermatology and Venereology. 2013;27:e263–e70.
13. National Institute for Health and Care Excellence. External genital and perianal warts: green tea (Camellia sinensis) leaf extract 10% ointment evidence summary. 2015.

This assessment is based on data submitted by the applicant company up to and including 12 February 2016.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.