Methyl aminolevulinate (Visonac) photodynamic therapy for acne vulgaris

**SUMMARY**

Methyl aminolevulinate (Visonac) is intended to be used for the treatment of moderate to severe acne vulgaris. If licensed, methyl aminolevulinate will offer an additional treatment option for this patient group. Visonac is used as part of a photodynamic therapy (PDT) that combines the application of a topical cream with controlled illumination by a red light source. The mechanism of action is two-fold: anti-bacterial effect against *Propionibacterium acnes* and a reduction of sebum production by the sebaceous glands.

Acne vulgaris is most prevalent among adolescents and young adults, affecting approximately 80% of people at some point between 11-30 years. Peak incidence is seen in females 14-17 and males 16-19 years. Complications arising from acne include scarring, hyperpigmentation and considerable psychological problems. Scarring is present in up to 90% of people who attend a dermatologist, but is usually mild and only visible under scrutiny with bright lights. However, significant scarring (socially noticeable) is estimated to occur in about one in five people with acne. The cosmetic appearance of acne, or scars caused by acne, can lead to significant psychological problems.

Depending on the severity of the condition, treatment may typically include topical antimicrobials (benzoyl peroxide), topical antibiotics, topical retinoids (isotretinoin, tretinoin, adapalene), comedolytics (azelaic acid), topical keratolytics (salicylic acid) and oral antiandrogens. For particularly severe forms of acne, oral antibiotics (tetracycline, oxyteracycline, doxycycline, lymecycline, erythromycin) may be used. Visonac is currently in a number of phase II clinical trials comparing its effect on facial lesions against treatment with placebo.
TARGET GROUP

- Acne vulgaris: moderate to severe.

TECHNOLOGY

DESCRIPTION

Methyl aminolevulinate (Visonac) is used as part of a photodynamic therapy (PDT) that combines the application of a topical cream with controlled illumination by a red light source. The mechanism of action is two-fold: anti-bacterial effect against *P. acnes* and a reduction of sebum production by the sebaceous glands. Visonac (80mg/g or 8% methyl aminolevulinate) is applied on clean skin and left for 1.5 hours under occlusion before illumination at 37 J/cm² and involves 4 treatments, each 2 weeks apart, at weeks 0, 2, 4 and 6.

Methyl aminolevulinate is currently licensed for use in non-hyperkeratotic and non-pigmented actinic keratosis, superficial and/or nodular basal cell carcinoma and squamous cell carcinoma in situ (Bowen's disease). Common recognised adverse effects (>10%) include disorders of the skin and subcutaneous tissue such as pain, burning sensation, scab and erythema.

INNOVATION and/or ADVANTAGES

If licensed, methyl aminolevulinate will offer an additional treatment option for this patient group.

DEVELOPER

Photocure ASA.

AVAILABILITY, LAUNCH OR MARKETING

In phase II clinical trials.

PATIENT GROUP

BACKGROUND

Acne vulgaris is a chronic skin condition in which blockage or inflammation of the hair follicles and accompanying sebaceous glands (known as pilosebaceous units) occurs. It principally affects the face (99% of people), the back (60%), and the chest (15%), and usually begins around the age of puberty². Complications arising from acne include scarring, hyperpigmentation and considerable psychological problems². Scarring is present in up to 90% of people who attend a dermatologist, but is usually mild and only visible under scrutiny with bright lights. However, significant scarring (socially noticeable) is estimated to occur in about one in five people with acne². The cosmetic appearance of acne, or scars caused by acne, can lead to significant psychological problems². A UK study of acne patients aged 16 and over attending a dermatology outpatient department found levels of social and emotional problems comparable with those in people with severe chronic disabling diseases, such as arthritis and epilepsy⁴.
None identified.

Acne vulgaris is most prevalent among adolescents and young adults, affecting approximately 90% of people at some point between 11-30 years\(^5\). Peak incidence is seen in females 14-17 and males 16-19 years\(^6\). A retrospective cohort study conducted in north-east England found that acne was the presenting problem in 3% of GP consultations in the 13-25 years age group\(^6\). It also found that in total, 55% of patients had two or more different prescriptions for acne and 8.5% were referred to a dermatologist\(^6\). Furthermore it found the average age a person presents with acne is about 15 years of age in males and 16 years of age in females\(^6\).

Depending on the severity of the condition, treatment may typically include topical antimicrobials (benzoyl peroxide), topical antibiotics, topical retinoids (isotretinoin, tretinoin, adapalene), comedolytics (azelaic acid), topical keratolytics (salicylic acid) and oral antiandrogens. For particularly severe forms of acne, oral antibiotics (tetracycline, oxytetracycline, doxycycline, lymecycline, erythromycin) may be used\(^8\),\(^9\),\(^10\).

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>Source of information</th>
<th>Location</th>
<th>Design</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00933543, PC TA204/09; Visonac vs placebo; phase II.</td>
<td>Photocure ASA.</td>
<td>Complete but unpublished.</td>
<td>Trial registry 11, press release 12, company.</td>
<td>USA and Canada.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=107; aged 9-35 years; moderate to severe acne vulgaris.</td>
</tr>
<tr>
<td>NCT00673933, PC TA203/08; Visonac vs placebo; phase II.</td>
<td>Photocure ASA.</td>
<td>Complete but unpublished.</td>
<td>Trial registry 11, company.</td>
<td>USA.</td>
<td>Randomised, placebo-controlled.</td>
<td>n=20; aged 15-40 years; skin type V or IV (Fitzpatrick scale); moderate to severe</td>
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</tbody>
</table>
acne vulgaris.

Schedule

Randomised to 4 treatments of Visonac or placebo, both topical, in conjunction with red light illumination, with 2 weeks between treatments.

Randomised to 4 treatments of Visonac or placebo, both topical, in conjunction with red light illumination, with 2 weeks between treatments.

Follow-up

Active treatment period 6 weeks (treatment at week 0, 2, 4 and 6). Follow-up visit 6 weeks after last treatment.

Active treatment period 6 weeks (treatment at week 0, 2, 4 and 6). Follow-up visit 6 weeks after last treatment.

Primary outcome/s

Success (improvement of at least 2 grades from baselines) according to the dichotomised investigator's global assessment (IGA); inflammatory lesion count (nodules, papules and pustules) and non-inflammatory count (open and closed comedones).

Hyperpigmentation and hypopigmentation.

Secondary outcome/s

Proportion of patients with success (excluding lesions on nose).

Erythema score after first PDT; inflammatory lesions; non-inflammatory lesions; erythema score after second PDT; erythema score 1 day after first treatment.

Key results

For Visonac vs placebo respectively:
Success rate, 9.3% vs 1.9% (p=0.07); median inflammatory lesion count at week 6, 42.2% vs 22.4% (p=0.0325); a similar pattern was shown for non-inflammatory lesions at week 6 although the difference between groups was not significant; median inflammatory lesion count at week 12, 39.8% vs 38.5% (p>0.05); non-inflammatory lesions, 36.3% vs 33.3% (p>0.05).

No patients developed hyperpigmentation or hypopigmentation in either treatment groups.

Adverse effects (AEs)

Low frequency of pain and erythema.

The frequency of AEs in areas treated with Visonac PDT was twice that for areas treated with vehicle cream (26 vs 13 events). The profile of AEs reported for areas treated with Visonac PDT was consistent with clinical experience. The most common treatment site AEs were skin warmth, erythema and pruritus.

Trial

NCT01347879, PC TA206/11; Visonac vs placebo; phase II.

NCT00594425, PC TA202B/06; Visonac vs placebo; phase II.

Sponsor

Photocure ASA.

Photocure ASA.

Status

Complete but unpublished.

Complete but unpublished.

Source of information

Trial registry14, press release15, company.

Trial registry16, company.

Location

USA.

USA.

Design

Randomised, placebo-controlled.

Randomised, placebo-controlled.

Participants

n=153; aged 12-35 years; severe acne vulgaris (IGA score 4).

n=190; aged 15-40 years; moderate to severe acne (IGA score 3-4); skin type I to IV (Fitzpatrick scale).

Schedule

Randomised to 4 treatments of Visonac PDT or placebo PDT every 2 weeks

Randomised to 4 treatments of Visonac 4% or 8% PDT or placebo PDT every 2 weeks.

Follow-up

Active treatment period 6 weeks (treatment at week 0, 2, 4 and 6). Follow-up visit 6 weeks after last treatment.

Active treatment period 6 weeks (treatment at week 0, 2, 4 and 6). Follow-up visit 12 weeks after last treatment.
<table>
<thead>
<tr>
<th>Primary outcome/s</th>
<th>Facial inflammatory lesion count (nodules, papules and pustules) 12 weeks after first treatment.</th>
<th>Facial inflammatory lesion counts (nodules, papules, and pustules) from baseline; success, defined as improvement of at least 2 grades from baseline according to the IGA scale based on facial assessment</th>
</tr>
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<tbody>
<tr>
<td>Secondary outcome/s</td>
<td>Success (improvement of at least 2 grades from baselines) according to IGA; facial non-inflammatory lesion count (open and closed comedones).</td>
<td>Reduction in facial non-inflammatory lesion counts.</td>
</tr>
<tr>
<td>Key results</td>
<td>For Visonac vs placebo respectively: reduction in inflammatory lesions, 43.8% vs 26.6% (p=0.003); success rate, 44.0% vs 26.4% (p=0.013). No difference between the two treatment groups with respect to the non-inflammatory lesions.</td>
<td>For Visonac 4% vs Visonac 8% vs placebo respectively: reduction in inflammatory lesions, 52%, 57% and 46%; non-inflammatory lesions, 41%, 47% and 33%; both Visonac groups were superior to the placebo group for non-inflammatory and total lesion counts; success rate, 17.5%, 21.2% and 14.3% (p&gt;0.05).</td>
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<tr>
<td>Adverse effects (AEs)</td>
<td>A higher number of patients receiving Visonac experienced local transient pain during illumination. Post treatment erythema reported more frequently in Visonac than placebo group (89% vs 70%).</td>
<td>For Visonac 4% vs Visonac 8% vs placebo respectively: treatment site AEs, 100%, 96% and 62%, severe intensity AEs, 6%, 4% and 2%. Most common reported AEs were application site erythema, application site pain, application site irritation and application site pruritus.</td>
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ESTIMATED COST and IMPACT

COST

The cost of Visonac is not yet known. The cost of other selected treatments for moderate to severe acne can be seen below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Unit cost*</th>
</tr>
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<tbody>
<tr>
<td>Benzoyl peroxide</td>
<td>Applied 1-2 times daily.</td>
<td>Cream, 5% net price 40g=£1.69</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Applied 1-2 times daily.</td>
<td>Gel, 0.01% net price 60g=£5.28</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500mg twice daily</td>
<td>250mg 28 tab pack=£13.35</td>
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IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other
- No impact identified

Impact on Services

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other
- None identified
**Impact on Costs**

- **Increased drug treatment costs**
- **Reduced drug treatment costs**
- **Other increase in costs: need for visits for illumination therapy.**
- **Other: uncertain unit cost compared to existing treatments**
- **None identified**

**Other Issues**

- **Clinical uncertainty or other research question identified**
- **None identified**

**REFERENCES**