North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

<table>
<thead>
<tr>
<th>Verdict:</th>
<th>Treatment guideline for the management of acne.</th>
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</thead>
<tbody>
<tr>
<td>Formulary inclusion:</td>
<td>Differin®, Epiduo®, Isotrex®, Skinoren®, Duac®, Treclin®, Aknemycin plus®, Isotrexin®, lymycline, clarithromycin and doxycycline are to be added to the North Staffordshire Joint Formulary</td>
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<tr>
<td>Formulary category:</td>
<td>Green</td>
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<tr>
<td>Restrictions:</td>
<td>N/A</td>
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<tr>
<td>Reason for inclusion:</td>
<td>The committee was satisfied with the evidence for various products for the management of acne and the ‘at a glance guide’.</td>
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</table>

Review summary:

**Formulary application:** Differin®, Epiduo®, Isotrex® and Skinoren®, Duac®, Treclin®, Aknemycin plus®, Isotrexin®, Tetralsyal and Doxycycline was reviewed for inclusion on the North Staffordshire Joint Formulary by the New Medicines Committee; Dr Nicholas Craven (Consultant Dermatologist) attended the meeting on 8th March 2016 to support the application.

**Licensed indications:**

Differin®, Epiduo®, Isotrex®, Skinoren® are indicated for the treatment of comedonal acne. Duac®, Treclin®, Aknemycin plus® and Isotrexin® are indicated for the treatment of mild papular/pustular acne. Tetralsyal® and Doxycycline are indicated for the treatment of moderate inflammatory acne.

**Related guidance:** NICE Clinical Knowledge Summary¹ Scottish Medicines compendium:

**Background information:**

Acne is the most common skin condition affecting young people. The treatment of acne is generally determined by the severity and extent of the condition. Mild and moderate acne is generally treated with topical agents including benzoyl peroxide, retinoids and antibiotics either alone or in combination. In moderate acne, oral treatment with antibiotics or anti-androgens may also be needed.

**Efficacy:**

This review is based on a number of studies. In a randomised study which compared topical adapalene with tretinoin, adapalene gel was superior to tretinoin gel with respect to reduction in inflammatory lesion counts (32% vs. 17% respectively, P=0.001) and total lesion counts (28%vs 22% respectively; P=0.042). Adapalene does not contain an antibiotic.² A randomized double-blind placebo controlled trial investigated Epiduo with adapalene alone, benzoyl peroxide alone or vehicle for 12 weeks. The study found that Epiduo was significantly more effective than corresponding monotherapies in total success (subjects ‘clear’ or ‘almost clear’).³ Isotretinoin had similar efficacy to benzoyl peroxide and significantly reduced non-inflammatory lesions at 4 (P=0.05), 8 (P<0.01) and 12 (P<0.01) weeks.⁴ In a randomised double blind placebo controlled study which evaluated the efficacy of azelaic acid (Skinoren®) gel in the treatment of mild to moderate acne vulgaris, it was found that that total lesion count was reduced by 60.6% and 19.9% by azelaic acid gel and the placebo respectively (P=0.002). Acne severity index (ASI) was reduced by by azelaic acid gel compared to placebo (65.2% and 21.3% p=0.001) respectively.⁵

NICE CKS recommends fixed dose combinations of topical antibiotic/topical retinoid/benzoyl peroxide (e.g. Duac®, Treclin®, Epiduo®, Aknemycin Plus®, Isotrexin gel®) for the treatment of mild papular/pustular acne. One study compared the effect of topical clindamycin phosphate, topical benzoyl peroxide and combination of two.⁶ The study found no significant difference in terms of efficacy when the effect of each treatment was compared. A cochrane review of 358 subjects with moderate to moderately severe acne vulgaris who received once-daily treatment with clindamycin 1%-benzoyl peroxide 5% for 11 weeks found that the treatment reduced inflammatory lesions by 53% and non-inflammatory lesions by 25%. Good or excellent global response was experienced in 50% of subjects. Overall tolerance ratings were good to excellent in 99% of subjects, and, except for mild to moderate expected local reactions, there were no adverse events related to treatment.⁷

Another trial also compared Duac Once Daily 10 mg/g + 30 mg/g Gel with clindamycin 1 % in vehicle gel, benzoyl peroxide 3 % in vehicle gel, and vehicle gel alone. Duac Once Daily 10 mg/g + 30 mg/g Gel was superior to clindamycin gel, benzoyl peroxide 3% gel, and vehicle gel in the proportion of subjects who had at least a 2-grade improvement in Investigator’s Static Global Assessment (ISGA) scale. Duac Once Daily 10 mg/g + 30 mg/g Gel was superior to clindamycin gel and vehicle gel in the absolute reduction of inflammatory, non-inflammatory, and total lesions, and was superior to benzoyl peroxide 3 % gel in the absolute reduction of inflammatory and total lesions. Secondary endpoints showed that the percentage reduction in

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All lesion counts from baseline to week 12 for Duac Once Daily 10 mg/g + 30 mg/g Gel was superior to clindamycin 1% gel and vehicle gel and the percentage reduction in inflammatory lesions was superior to benzoyl peroxide 3% gel. The safety and efficacy of Isotrexin® was evaluated in a double-blind, randomised, placebo-controlled trial in 161 patients with mild to moderate acne vulgaris. Isotrexin® was compared with an erythromycin 2% gel, isotretinoin 0.05% gel and a placebo gel. Efficacy was assessed by comparison between the groups of the total number of lesions, total number of inflammatory lesions, total number of non-inflammatory lesions, acne severity grade, global change scores (investigator assessment) and the patient's self-rating assessment of their condition. Isotrexin® gel produced the greatest improvement for all acne assessments at week 12 when compared to erythromycin 2% gel alone, isotretinoin 0.05% gel alone and placebo. Isotrexin® significantly (p<0.05) reduced the mean total lesions (inflammatory and non-inflammatory) when compared with placebo.

A post-marketing surveillance study involving over 6500 patients investigated the efficacy and tolerability of topical erythromycin/tretinoin combination preparation in acne treatment in 6500 patients. Efficacy of tretinoin-erythromycin was classed as 'very good' (42.8%) or 'good' (43.3%) in 86.1% of all patients treated. Efficacy and tolerability of a gel preparation with 0.025% tretinoin and 4% erythromycin in acne vulgaris was also evaluated in an open multicentre study. Treatment with erythromycin/tretinoin resulted in a reduction of lesions after 2 weeks in 35% of the patients with comedones eliminated in 47.0% at the end of study. Papules were eliminated and improved in 58.2% and 32.6% patients and pustules in 74.3% and 18.3% respectively.

Three randomised double-blind studies resulted in Treclin® statistically reducing number of lesions compared to tretinoin, clindamycin and tretinoin vehicle. Failure rates were also statistically significantly lower with Treclin (80%) compared to tretinoin (85%), clindamycin (85%) and tretinoin vehicle (91%) (P < 0.05). For the Global Severity Score (clear/almost clear) at week 12, Treclin had the greatest success (20%) compared to clindamycin (15%), tretinoin (15%) and vehicle (9%) (P < 0.05). NICE clinical knowledge summary recommends systemic antibiotics for treatment of moderate inflammatory acne. Oxytetracycline, doxycycline, or lymecycline are recommended as first-line options with erythromycin an alternative if tetracyclines are poorly tolerated or contraindicated (such as in pregnancy). Minocycline is not recommended. Doxycycline and lymecycline are once daily preparations.

A systematic review on oral tetracyclines (oxytetracycline, lymecycline, doxycycline and minocycline) for the treatment of inflammatory acne found no significant difference between the oral tetracyclines in terms of improvement in inflammatory (32 trials, P = 0.898) and non-inflammatory (23 trials, P = 0.429) lesions. No trials are currently available which compare lymecycline with placebo. A randomized, double-blind, phase 2 dose-ranging study in subjects with moderate to severe inflammatory acne evaluated the safety and efficacy of three doses of doxycycline compared with placebo in the treatment of moderate to severe inflammatory facial acne vulgaris. A dose-response effect was seen with doxycycline in subjects with moderate to severe inflammatory acne. The highest dose group (corresponding to approximately 2.4 mg/kg/day) showed a statistically significant difference from placebo.

**Safety:** contraindications & Adverse effects please see individual SPC for detail.

**References:**

1. NICE Clinical Knowledge summaries: Acne Vulgaris [http://cks.nice.org.uk/acne-vulgaris#isenario:1](http://cks.nice.org.uk/acne-vulgaris#isenario:1)
2. Grosshans, E., Marks, R., Mascaro, et al. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *British Journal of Dermatology* 1998;139: 26-33. 10.1046/j.1365-2133.1998.13902026.x
3. Evaluation of clinical efficacy and safety of adapalene 0.1% gel versus tretinoin 0.025% gel in the treatment of acne vulgaris, with particular reference to the onset of action and impact on quality of life. *British Journal of Dermatology* 1998; 139, pp26–33
8. Summary of product characteristics (SPC).Duac Once Daily 10mg/g + 50mg/g Gel. Stiefel. Last Updated on eMC 26-Jan-2015. [https://www.medicines.org.uk/emc/medicine/13513](https://www.medicines.org.uk/emc/medicine/13513)
9. Isotrexin gel® SPC: [https://www.medicines.org.uk/emc/medicine/7495](https://www.medicines.org.uk/emc/medicine/7495)

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