Oral alitretinoin for adults with chronic hand eczema

Target group
- Chronic hand eczema (dermatitis) - adults who are refractory to topical corticosteroids.

Background
Hand eczema (synonymous with dermatitis) is a chronic skin condition that can cause severe morbidity in adults with severe itching, and soreness and pain, especially when deep cracks develop in areas of chronic disease. Itching can cause sleep loss and also interfere with employment. In the acute stage, hand eczema is characterised by redness and an accumulation of fluid beneath the skin surface (vesicles). In the chronic stage, thickening, and scaling and dryness of the skin develop. Hand eczema can present in different phenotypes, often involves the dorsal hands and fingers, but may extend to the wrists, with ill-defined, thin, light pink, xerotic and lichenified plaques. Chronicity can lead to decreased mobility of the fingers1,2.

Causes of hand eczema are usually a combination of predisposing factors such as a previous history of atopic disease (eczema, asthma and hay fever) superimposed with external contact factors. Exogenous hand eczema (hand eczema due to identified external factors) can either be irritant, contact dermatitis (caused by repeated exposure to water and irritants), or allergic contact dermatitis (due to a specific allergy such as rubber, chromium or nickel). Sometimes an external cause is not obvious and such eczemas are classified as ‘endogenous’ and may be further classified as atopic hand eczema or dyshidrotic hand eczema, or pompholyx. Genetic factors are probably important in addition to atopy3.

The social stigma of visible disease, the need for frequent visits to the doctor, and to regularly apply greasy applications all add to the burden of the disease. Hand eczema is the most important occupational skin disease especially in occupations that involve a lot of wet work such as nursing, hairdressing, and food preparation. Other occupations, such as builders and printers, are also at high risk of developing hand eczema, mainly due to friction and irritation rather than specific allergic sensitisation.

Technology description
Alitretinoin is a derivative of retinoic acid (9-cis-retinoic acid), an endogenous (physiological) retinoid, which binds to and activates intracellular retinoid receptor subtypes Retinoic Acid Receptors (RARs) and Retinoid X Receptor (RXR). Once activated these receptors regulate the expression of genes that control the process of cellular differentiation and proliferation in both normal and neoplastic cells. It is anticipated that alitretinoin will be administered orally at doses of 10-30 mg once daily.

Topical alitretinoin is available in the US and Europe as Panretin Gel 0.1% for the topical treatment of cutaneous lesions of patients with AIDS-related Kaposi’s sarcoma (KS).

Other oral retinoids such as acitretin for psoriasis and isotretinoin for acne are licensed in Europe4.

Innovation and/or advantages
There are currently no drugs licensed specifically for chronic hand eczema refractory to topical corticosteroids. If licensed, alitretinoin would become the first specific drug treatment for this condition.
Developer
Basilea Pharmaceutica AG.

Place of use
☐ Home care e.g. home dialysis
☐ Community or residential care e.g. district nurses, physio
☐ Secondary care e.g. general, non-specialist hospital
☐ Tertiary care e.g. highly specialist services or hospital
☐ General public e.g. over the counter
☐ Other:

Availability, launch or marketing dates, and licensing plans:
The licence application was submitted for European approval in October 2007.

Relevant guidance

Clinical need and burden of disease
There are no specific epidemiological data for hand eczema in England and Wales. International estimates range between 2% to 11% (equating to 820,000 to 4,510,000 patients in England and Wales). Approximately 50% of all patients with hand eczema seek dermatological treatment and of these around 7% of patients with hand eczema have severe, chronic disease and approximately 2-4% may be refractory to topical treatment (equating to an estimated 574 to 6320 patients in England and Wales).

Existing comparators and treatments
Current management options for chronic atopic eczema in adults include:
• Identification and avoidance of contributory factors e.g. known irritants or allergens
• Emollients – regular and liberal use
• Corticosteroids oral and topical (sometimes with occlusion under cling film overnight)
• Antimicrobial therapy – to treat and prevent skin infections
• Antihistamines – to reduce itching
• Oral immunosuppressives (e.g. ciclosporin and azathioprine)
• Calcineurin inhibitors (e.g. tacrolimus or pimecrolimus)
• Where vesicles are present, hands are soaked in dilute potassium permanganate solution (or aluminium hydroxide solution which does not stain nails brown)
• UV irradiation (e.g. UVB, UVA, PUVA)

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Prospective trial</th>
<th>BACH study</th>
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<tbody>
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<td>mA</td>
<td>Study completed. Poster presentation.</td>
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<td>Location</td>
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<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo-controlled, prospective trial.</td>
<td>Prospective, randomised, double-blind, placebo-controlled.</td>
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<td>Participants in trial</td>
<td>n=319, 18-70 years (excluding women of childbearing potential), moderate or severe</td>
<td>n=1032, 18-75 years, severe chronic hand eczema determined by PGA,</td>
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severe (of at least 3 months duration) refractory or intolerant of topical corticosteroids, chronic hand dermatitis. Randomised to: placebo or 10 mg, 20 mg or 40 mg of oral alitretinoin, taken once daily for 12 weeks. Patients also applied emollient.

refractory to topical steroids. Randomised to alitretinoin 10 mg (n=418) or 30 mg (n=409), or placebo (n=205) once daily. Patients provided with emollient. No concomitant topical or systemic mediation allowed.

| Follow-up | 4 weeks for safety; additional 3 months for relapse rate. | 12 or 24 weeks depending on treatment response |
| Primary outcome | Physician’s global assessment (PGA) of overall chronic hand dermatitis severity. | Overall treatment response, efficacy and tolerability. |
| Secondary outcomes | Safety, total lesion symptom score (TLSS), patient’s global assessment (PaGA) of improvement and extent of the disease, relapse | PaGA, disease extent, treatment response time, modified total lesion symptom score. |
| Key results | Significant and dose-dependent improvement in disease status with alitretinoin. Patient responses to placebo (assessed by PGA), 10 mg, 20 mg or 40 mg alitretinoin dose: 27%, 39%, 41% and 53% respectively. Three months after discontinuation, relapse rate was 26%, independent of dose. | Dose-dependent response rate observed. Both dosage regimens were superior to placebo. Patient response rate for each treatment group according to PGA (clear or almost clear hands) at end of therapy: 30 mg group was 47.7% and 10 mg was 28%, compared to placebo 16.6%. |
| Major adverse effects | 75 patients (24%) withdrew, 25 due to adverse events: headache, flushing, mucocutaneous events, hyperlipidaemia, and decreased haemoglobin and free thyroxin levels. | Most common: headache, mucocutaneous effects, decreased thyroid stimulating hormone (TSH) levels and hyperlipidaemia. |

Trial name | Re-treatment study\textsuperscript{16} Phase III - extension | Open label study\textsuperscript{17} Phase III – extension |
| Sponsor | Basilea | Basilea |
| Status | Study completed. Poster presentation. | Study completed. Poster presentation. |
| Location | Europe and Canada | Europe and Canada |
| Participants in trial | n=117 patients who responded in BACH study and relapsed (defined as minimum TLSS score of 75%) within 24 weeks. Allocated to their previous treatment or placebo. Patients provided with emollient. No concomitant topical or systemic mediation. | n=248 patients, 18-75 years, severe chronic hand eczema (determined by PGA for at least 6 months), refractory to topical steroids. Received alitretinoin 30 mg once daily for 24 weeks. |
| Follow-up | 12 or 24 weeks | 24 weeks |
| Primary outcome | PGA, overall treatment response, efficacy and tolerability. | Safety |
| Secondary outcomes | PaGA, disease extent, treatment response time, modified total lesion symptom score at 12 or 24 weeks. | Efficacy |
| Key results | Among previous responders, those retreated with alitretinoin had substantially higher response rates than those given placebo: 10 mg and 30 mg was 38.1% and 75.5% respectively compared to <10% for placebo. | Adverse effects reported for \(\geq 2\%\) of patients given 30 mg alitretinoin, most frequent were headache (17.3%), nasopharyngitis (8.1%) and flushing (4.8%). |
Estimated cost and cost impact

The unit cost of alitretinoin is yet to be determined. An additional cost to administration of alitretinoin will be pregnancy prevention measures, as retinoids are teratogenic.

Potential or intended impact – speculative

Prescription is likely to be limited to specialist clinicians with an understanding of the risks and monitoring associated with systemic retinoids.

Patients

☑ Reduced morbidity
☐ Reduced mortality or increased survival
☐ Other:
☐ Non identified

☐ Quicker, earlier or more accurate diagnosis or identification of disease
☐ Other:
☐ Non identified

Services

☑ Increased use: New treatment option therefore more patients may present for treatment
☐ Service reorganisation required
☐ Staff or training required
☐ Other:
☐ Non identified

☐ Decreased use
☐ Other:
☐ Non identified

Costs

☐ Increased unit cost compared to alternative
☐ New costs: New treatment option
☐ Increased costs: more patients coming for treatment
☐ Increased costs: capital investment needed
☐ Savings:
☐ Other:

References