House dust mite allergen immunotherapy tablet (Mitizax) for house dust mite allergy-induced rhinitis and conjunctivitis – third line

SUMMARY

House dust mite (HDM) allergen immunotherapy tablet (Mitizax) is intended to be used as a third line therapy for the treatment of house dust mite allergy-induced rhinitis and conjunctivitis. If licensed, HDM allergen immunotherapy tablet may provide a treatment option for allergic rhinitis and rhinoconjunctivitis, with the potential for delivering disease modifying allergen immunotherapy without the disadvantages and risks of subcutaneous immunotherapy. HDM allergen immunotherapy tablet contains a 1:1 mixture of allergen extract from *Dermatophagoides pteronyssinus* and allergen extract from *Dermatophagoides farina*.

Allergic rhinitis has the highest prevalence of all allergic respiratory diseases, affecting over 20% of the UK population (equating to over 12 million people), and 400 million people worldwide. Over 56% of allergic rhinitis patients in the UK presenting for routine care have moderate or severe disease, and 52% have persistent disease. Allergic conjunctivitis is strongly associated with allergic rhinitis with around 90% of people with allergic rhinitis experiencing at least one day of ocular symptoms per week. In a retrospective review of European patients with allergic rhinitis symptoms, of the 31.6% of patients who were sensitive to at least one identifiable allergen, the most common sensitivity was to HDMs (62.1%). Allergic rhinitis is closely linked to other inflammatory conditions, and epidemiological evidence has repeatedly shown the co-existence of rhinitis and asthma.

Allergen avoidance is recommended as first-line treatment for allergic rhinitis, followed by pharmacotherapy aimed at symptom control (mainly antihistamines and topical nasal corticosteroids). For patients with more severe disease, who do not respond to usual therapy, specific immunotherapy is recommended. HDM allergen immunotherapy tablet is currently in phase III clinical trials comparing its effect on allergy symptoms and use of symptomatic medication against treatment with placebo. The main trial is expected to complete in April 2013.
TARGET GROUP

• Rhinitis and conjunctivitis: House Dust Mite (HDM) allergy-induced – third line.

TECHNOLOGY

DESCRIPTION

House dust mite allergen immunotherapy tablet (Mitizax) contains a 1:1 mixture of allergen extract from *Dermatophagoides pteronyssinus* and allergen extract from *Dermatophagoides farinae* and is intended for the treatment of allergic rhinitis and rhinoconjunctivitis. It is a rapidly dissolving sublingual tablet, dissolving on the tongue in less than 3 seconds. Specific allergen immunotherapy is the only treatment modality with the potential to change the natural course of allergic disease; perennial indoor HDMs are a major source of allergens involved in rhinitis, rhinoconjunctivitis and asthma. Among some 50,000 species of mites currently identified, two perennial indoor HDM, *D. pteronyssinus* and *D. farina*, are responsible for sensitisation in most patients.

Specific allergen immunotherapy is currently recommended, but not licensed, for the treatment of allergic rhinitis patients that are intolerant to standard pharmacotherapy, or have failed to achieve adequate relief of symptoms despite treatment with intranasal corticosteroids and/or antihistamines. The subcutaneous (SC) administration of allergen immunotherapy can be uncomfortable and time-consuming; local adverse events such as injection site itch or swelling are fairly common, and although rare, systemic reactions can be severe. Sublingual immunotherapy (SLIT) may be associated with a lower incidence of systemic reactions. HDM allergen immunotherapy tablet is administered sublingually at 6 or 12 development units (DU) daily.

*D. pteronyssinus* AIT is in a phase III clinical trial for the treatment of asthma.

INNOVATION and/or ADVANTAGES

If licensed, HDM allergen immunotherapy tablet may provide a treatment option for allergic rhinitis and rhinoconjunctivitis with the potential for delivering disease modifying allergen immunotherapy without the disadvantages and risks of SC immunotherapy.

DEVELOPER

Alk-Abelló.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Rhinitis is characterised by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching. Symptoms occur during two or more consecutive
days for more than 1 hour on most days. Allergic rhinitis is the most common form of non-infectious rhinitis and is associated with an immunoglobulin E (IgE)-mediated immune response to specific allergens. It is often associated with ocular symptoms, with allergic conjunctivitis often accompanying allergic rhinitis.

Allergic rhinitis is classified by the severity (mild or moderate to severe) and persistence (intermittent or persistent) of symptoms. Symptoms are defined as ‘mild’ if all of the following apply: normal sleep, no impairment of daily activities, no impairment of sport or leisure, no impairment of work or school, and symptoms present but not troublesome; and ‘moderate to severe’ if one or more of the following apply: sleep disturbance, impairment of daily activities, impairment of sport or leisure, impairment of work or school, or troublesome symptoms.

‘Intermittent’ allergic rhinitis is defined as a symptom duration of <4 days per week or <4 consecutive weeks; and ‘persistent’ allergic rhinitis is defined as symptom duration of >4 days/week for >4 consecutive weeks.

CLINICAL NEED and BURDEN OF DISEASE

Allergic rhinitis has the highest prevalence of all allergic respiratory diseases, affecting over 20% of the UK population (equating to over 12 million people), and 400 million people worldwide. Over 56% of allergic rhinitis patients in the UK presenting for routine care have moderate or severe disease, and 52% have persistent disease, however this may be an underestimate. Allergic conjunctivitis is strongly associated with allergic rhinitis with around 90% of people with allergic rhinitis experiencing at least one day of ocular symptoms per week. Allergic rhinitis onset is typically under the age of 30, with a peak incidence in childhood and adolescence. HDMs are a common aeroallergen and cause of allergic rhinitis in the UK. HDM allergy is highly prevalent worldwide, with 20% of the population being affected and an extra 30% carrying asymptomatic HDM sensitisation; the prevalence of HDM sensitisation in the developed world is over 54%. In a retrospective review of European patients with allergic rhinitis symptoms, of the 31.6% of patients who were sensitive to at least one identifiable allergen, the most common sensitivity was to HDMs (62.1%). Around 20% of patients with allergic rhinitis are not adequately controlled on currently available pharmacotherapy and are therefore eligible for immunotherapy.

Allergic rhinitis is closely linked to other inflammatory conditions, and epidemiological evidence has repeatedly shown the co-existence of rhinitis and asthma; around 80% of asthma patients and 80% of children with eczema also suffer from allergic rhinitis. Mite allergy frequently starts with symptoms of rhinitis, but over the longer term many patients develop symptoms of asthma. Rhinitis represents a major cause of morbidity that includes interference with usual daily activities, impaired sleep quality, and may adversely affect mood. Those who are HDM allergic with co-morbid asthma, rhinitis and conjunctivitis experience a poor quality of life with numerous visits to the GP and emergency hospital services. Allergic rhinitis represents a significant healthcare burden; in 2004 treatment costs for allergic diseases and asthma accounted for 10% of all primary care prescribing costs, and direct UK National Health Service costs for managing allergic diseases were estimated at more than £1 billion per year. In 2012, there were 649 admissions for allergic perennial rhinitis (J30.3) in England, resulting in 54 bed-days and 650 finished consultant episodes.

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* Expert personal communication.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

No relevant guideline identified.

Other Guidance

- European Academy of Allergy and Clinical Immunology (EAACI). EAACI: A European Declaration on Immunotherapy. Designing the future of allergen specific immunotherapy. 2012\textsuperscript{12}.
- WHO Collaborating Center for Asthma and Rhinitis. Severe chronic allergic (and related) diseases: a uniform approach--a MeDALL\textsuperscript{b}--GA(2)LEN\textsuperscript{c}--ARIA\textsuperscript{d} position paper. 2012\textsuperscript{13}.
- GA(2)LEN–WHO Collaborating Center: Practical guide for skin prick tests in allergy to aeroallergens. 2012\textsuperscript{14}.
- British Society for Allergy & Clinical Immunology (BSACI). Immunotherapy for allergic rhinitis. 2011\textsuperscript{3}.
- BSACI. BSACI guidelines for the management of allergic and non-allergic rhinitis. 2008\textsuperscript{15}.
- ARIA. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). 2008\textsuperscript{4}.
- ARIA. Allergic rhinitis management pocket reference 2008. 2008\textsuperscript{5}.
- EAACI. Requirements for medications commonly used in the treatment of allergic rhinitis. 2003\textsuperscript{16}.

EXISTING COMPARATORS and TREATMENTS

The ARIA guidelines\textsuperscript{4,17} recommend allergen avoidance as first-line treatment for allergic rhinitis, followed by pharmacotherapy aimed at symptom control (mainly antihistamines and topical nasal corticosteroids). For patients with more severe disease, who do not respond to usual therapy, specific immunotherapy is recommended. Immunotherapy is the only disease-modifying treatment and can give long term benefits\textsuperscript{6}. Treatment options for allergic rhinitis include\textsuperscript{4,13,14,18,19}:

- Saline nasal douching.
- Oral and nasal H1-antihistamines – first-line therapy for intermittent and persistent symptoms – non-sedating (bilastine, desloratadine, rupatadine) or sedating (ketotifen).
- Oral decongestants – adjuvant, intermittent use – ephedrine, phenylephrine, phenylpropanolamine and pseudoephedrine.
- Intranasal decongestants – adjuvant, intermittent use – oxymethazoline, xylometazoline and ipratropium.
- Leukotriene antagonists (unlicensed for indication) – first-line therapy for intermittent and persistent symptoms – montelukast, pranlukast and zafirlukast.
- Topical cromones – first-line therapy for moderate to severe intermittent, and mild persistent symptoms – e.g. cromoglicate.

\textsuperscript{b} Mechanisms of the Development of ALLergy collaborative project.
\textsuperscript{c} Global Allergy and Asthma European Network.
\textsuperscript{d} Allergic Rhinitis and its Impact on Asthma.
\textsuperscript{e} Expert personal communication.
Nasal corticosteroids – first-line therapy for moderate to severe intermittent and persistent symptoms – mometasone, fluticasone, betamethasone, dexamethasone and budesonide.

Oral corticosteroids – second line therapy for moderate to severe persistent symptoms.

Specific allergen immunotherapy (unlicensed for indication) – third-line therapy for moderate to severe persistent symptoms.

- Sublingual *Dermatophagoides* extract – e.g. Der p 1 via Oralvac compact pump, Der p 1 and Der f 1g combination via Staloral300 pump.
- SC *Dermatophagoides* extract – e.g. Alutard SQ (*Dermatophagoides*).

Treatments for rhinoconjunctivitis in association with allergic rhinitis include:

- saline drops (mild cases).
- oral H1-antihistamines.
- intraocular H1-antihistamines – e.g. antazoline, azelastine.
- intraocular cromones – e.g. nedocromil.

### EFFICACY and SAFETY

<table>
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<tr>
<td>n=617; aged 5-55 years; allergic rhinitis; HDM-induced (with or without asthma) allergy; positive specific IgE; use of medication for the control of rhinoconjunctivitis.</td>
<td>Randomised to pangramin HDM SLIT HDM mix or placebo; all administered sublingually as an up-dosing phase (vial 0 to vial 4) and maintenance phase (3 times per week) for 12 months.</td>
<td>Active treatment for 12 months, follow-up at 1 week after last dose.</td>
<td>Rhinoconjunctivitis symptoms score, rhinoconjunctivitis medication score.</td>
<td>Rhinitis symptom score, conjunctivitis symptom score, asthma symptom score, number of days without rhinoconjunctivitis symptoms and without rescue medication, rhinoconjunctivitis visual analogue scale, rhinitis quality of life (QoL) questionnaire, global assessment of rhinoconjunctivitis symptoms after each phase.</td>
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<tr>
<td>n=900 (planned); aged 18-65 years; HDM allergy; positive specific IgE; use of symptomatic medication for treatment of HDM allergy.</td>
<td>Randomised to HDM SLIT 6 DU tablet, HDM SLIT 12 DU tablet, or placebo; all given sublingually, 1 tablet daily for 12 months.</td>
<td>Active treatment for 12 months, follow-up at 9 weeks after last dose.</td>
<td>Allergy symptoms, use of symptomatic medication.</td>
<td>-</td>
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5 *Dermatophagoides pteronissinus* derived allergen.
6 *Dermatophagoides farina* derived allergen.
7 Pangramin SLIT HDM is an aluminium hydroxide depot formulation of HDM extract.
Key results
Not reported.

Adverse effects (AEs)
Not reported.

Expected reporting date
Study completion date reported as Feb 2012.

Trial
NCT01700192, P05607, MK-8237-001; aged ≥12 years; HDM SLIT tablet vs placebo; phase III.

Sponsor
Merck.

Status
Ongoing.

Source of information
Trial registry**, manufacturer.

Location
USA.

Design
Randomised, placebo-controlled.

Participants
n=1,500 (planned); aged ≥12 years; HDM-induced allergic rhinitis or rhinoconjunctivitis (with or without asthma); ≥1 year duration.

Schedule
Randomised to HDM SLIT 12 DU, or placebo, both sublingually once daily; all with rescue medication as needed (epinephrine 0.3mg intramuscularly; loratadine tablet 10mg orally; olopatadine hydrochloride ophthalmic drops 0.1% intracocularly; mometasone furoate monohydrate nasal spray 50µg intranasally).

Follow-up
Active treatment for 12 months, follow-up for 2 weeks.

Primary outcome/s
Total combined daily symptom and medication scores, AEs, number of participants who discontinue study drug due to AEs.

Secondary outcome/s
Daily symptom score, visual analogue scale score, daily medication score, total nasal symptom score (TNSS).

Key results
Not reported.

AEs
Not reported.

Expected reporting date
Primary completion date reported as Feb 2015.

ESTIMATED COST and IMPACT

COST

The cost of HDM allergen immunotherapy tablet is not yet known. The 2010 costs of other selected immunotherapies (unlicensed in the UK) obtained from a BSACI survey of immunotherapy clinics in the UK are as follows 3:

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1. BSACI (British Society for Allergy and Clinical Immunology) 2010 Survey of Immunotherapy Clinics in the UK.
Drug | Dose | Annual cost
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Der p 1 via Oralvac Compact pump (Allergy Therapeutics). | 2.9µg sublingually, daily (3 pumps per day) for 8 months (0.71mg per year). | £629
Der p 1 and Der f 1 via Staloral300 pump (Stallergenes). | 120IR (~84µg) sublingually, daily; or 240IR (~168µg) sublingually three times weekly (30.7mg and 61.3mg per year, respectively). | £985
Alutard SQ (Dermatophagoides). | 25 injections (90µg Der p 1 allergen per year). | £1,359

**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- No impact identified

**Impact on Services**
- Increased use of existing services
- Decreased use of existing services: self-administration and use outside of specialist clinic 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:
- Other reduction in costs:
- Other: None identified

**Other Issues**
- Clinical uncertainty or other research question identified: None identified

**REFERENCES**


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Index of Reactivity (IR) defined as a measure of the allergenicity of an allergen extract. The allergen extract contains 100 IR/ml when, on a skin prick-test using a Stallerpoint, it induces a wheal diameter of 7mm in 30 patients sensitized to this allergen (geometric mean). The cutaneous reactivity of these patients is simultaneously demonstrated by a positive skin prick-test to either 9% codeine phosphate or 10mg/ml histamine.
7 Scadding GK and Williams A. The burden of allergic rhinitis as reported by UK patients compared with their doctors. Rhinology 2008;46(2):99-106.
9 Boulet LP, Turcotte H, Laprise C et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. Clinical and Experimental Allergy 1997;19(2):52-9.