Drugs 2001; 61 (2): 253-260
0012-6667/01/0002-0253/$27.50/0

Omalizumab

Stephanie Easthope and *Blair Jarvis*

Adis International Limited, Auckland, New Zealand.

Contents

Abstract

▲ Omalizumab is a recombinant humanised monoclonal antibody which specifically binds to the Cε3 domain of immunoglobulin (Ig) E, the site of high-affinity IgE receptor binding.

▲ Improvements in asthma symptoms and health-related quality-of-life, and a significant reduction in the frequency of asthma exacerbations were seen in allergic asthmatic patients treated with omalizumab.

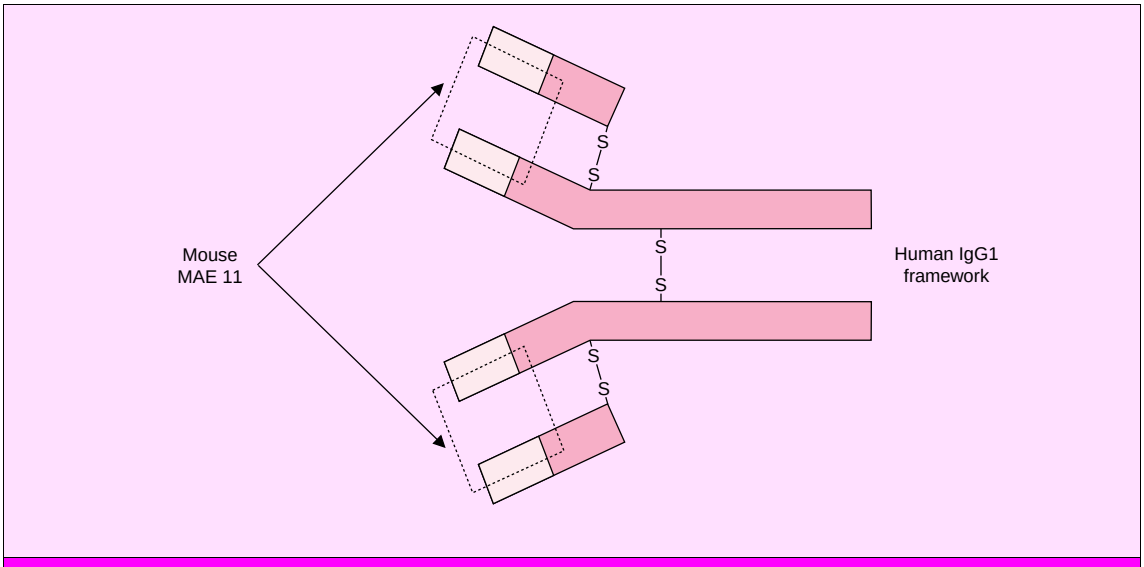
▲ Omalizumab was also effective in the treatment of children with allergic asthma demonstrating improvements in health-related quality-of-life and significant dosage reductions of inhaled corticosteroids.

▲ Administration of omalizumab to patients with allergic rhinitis resulted in a rapid dose-dependent suppression of serum free IgE levels.

▲ Omalizumab significantly improved health-related quality-of-life and nasal symptoms in patients with seasonal allergic rhinitis. Antihistamine requirements were also significantly reduced following treatment.

▲ Adverse events were infrequent in clinical trials of omalizumab, and not significantly different from placebo. The most frequent drug-related event was mild to moderate urticaria.

Features and properties of omalizumab (rhuMAb-E25)	
Indications	
Allergic asthma Allergic rhinitis	
Mechanism of action	
Recombinant humanised monoclonal anti-IgE antibody	Binds to Fc portion of IgE, blocking binding to mast cell receptor FcεR1
Dosage and administration in clinical trials	
Allergic asthma	150-300mg every 4 wks or 225-375mg every 2 wks (dependent on bodyweight and baseline IgE)
Allergic rhinitis	300mg every 3-4 wks (frequency dependent on baseline IgE)
Route of administration	Subcutaneous
Pharmacokinetic profile	
Peak plasma concentration (dosage)	30.9 mg/L (1 mg/kg IV)
Time to peak plasma concentration (dosage)	≤14 days (0.15 mg/kg SC)
Volume of distribution	Approximating plasma volume
Elimination half-life	1-4 weeks
Adverse events	
Drug-related	Mild urticaria



Allergic asthma and rhinitis are characterised by an early allergic response and chronic inflammation of the epithelium and submucosa of the airways.[1] Immunoglobulin (Ig) E plays a pivotal role in the development of allergic inflammation by binding to receptors on effector cells and triggering the release of inflammatory mediators.[2] Allergen-specific immunotherapy has been used in an attempt to reduce the allergic reaction but has had moderate clinical efficacy and so, for the majority of patients with asthma or rhinitis, the most effective treatment currently consists of local or systemic corticosteroids.[1]

Omalizumab, a monoclonal antibody directed against the high-affinity receptor binding domain of IgE, has been developed for the treatment of allergic asthma and seasonal allergic rhinitis and has been evaluated in a number of clinical trials.

1. Pharmacodynamic Profile

Mechanism of Action

• Omalizumab selectively binds to the Cε3 domain of IgE at the site of high-affinity IgE receptor (FcεR1) binding, thus blocking binding of IgE to effector cells and preventing the activation and subsequent release of cellular mediators.[3-5]

Effects on Serum IgE Levels

• Serum free IgE levels are rapidly suppressed in a dose-dependent manner following intravenous or subcutaneous administration of omalizumab (fig. 1) and correlate with improvements in clinical outcomes (section 3).[6-8]

• The formation of omalizumab-IgE complexes resulted in a significant 2- to 9-fold dose-dependent increase in total IgE levels (free IgE levels decreased).[7,9-13] Complex formation was not associated with abnormalities in renal function or other clinical evidence of immune complex disease.[10]

Effects on Bronchial Responses to Allergen Challenge

• Treatment with omalizumab significantly attenuated the early and late phase asthmatic airway responses to allergen challenge in randomised, double-blind trials in patients with allergic asthma.[10,12] The concentration of allergen required to cause a fall in forced expiratory volume

in 1 second (FEV_1) of 15% (PC_{15}) was significantly increased after 77 days of treatment with omalizumab (+2.7 *vs* –0.8 doubling doses from baseline for omalizumab *vs* placebo, $p \leq 0.002$).[12] The maximal FEV_1 decline at 2 to 7 hours (late phase) was reduced with omalizumab compared with placebo (9 *vs* 18% decline; $p < 0.02$) [baseline maximal FEV_1 decline was 24 and 20%, respectively].[10]

Effects on Induced Sputum and Circulating Lymphocytes

• In adults with allergic rhinitis the number of high-affinity IgE receptors on circulating basophils decreased from 230 000 to <10 000 receptors/basophil after 46 weeks' treatment with omalizumab.[14] *In vitro* studies showed that the number of receptors was regulated by levels of free IgE.[14]

• Eosinophil and neutrophil numbers in induced sputum and blood eosinophil levels of omalizumab-treated patients were not significantly different from those of placebo recipients in clinical trials.[10,15,16]

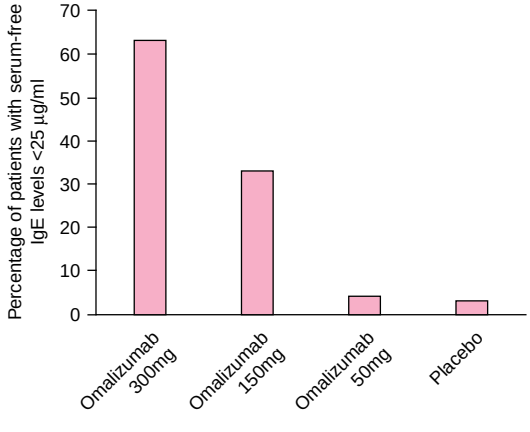


Fig. 1. Patients with serum free immunoglobulin (Ig) E levels <25 µg/ml after treatment with omalizumab. 536 patients with seasonal allergic rhinitis were administered omalizumab or placebo subcutaneously 3 or 4 times in a 12-week randomised, double-blind trial.[6]

2. Pharmacokinetic Profile

• The mean maximum concentration of omalizumab at steady state was 30.9 mg/L following an initial dosage of 2.0 mg/kg, and 6 subsequent dosages of 1.0 mg/kg administered intravenously over 77 days to adult patients with allergic asthma.[12]

• The serum omalizumab concentrations following subcutaneous or intravenous administration of single or multiple doses was described by a 2-compartment model with a volume of distribution approximating plasma volume (quantitative data were not reported in this abstract).[17] The pharmacokinetic profile of omalizumab was similar in adults, adolescents and children.[13,17]

• Trough concentrations of omalizumab in patients with allergic rhinitis were similar when the drug was administered intravenously or subcutaneously; however, there was a slow absorption phase over several days with peak serum concentrations of >2 mg/L reached by 14 days after subcutaneous administration of omalizumab 0.15 mg/kg.[7]

• Omalizumab was cleared slowly from circulation with a terminal elimination half-life of 1 to 4 weeks.[7,9,13,17]

• No specific uptake into any tissue or organ was demonstrated in cynomolgus monkeys, with 92% of a single intravenous dose of ^{125}I-labelled omalizumab being found in the blood 4 days after administration.[18]

3. Clinical Trials

The therapeutic efficacy of omalizumab has been evaluated in multicentre, randomised, double-blind, placebo-controlled, parallel-group studies in children (aged ≥6 years), adolescents and adults with allergic asthma,[11,19,20] and in adolescents and adults (aged ≥12 years) with seasonal allergic rhinitis.[7,8,21,22] Some studies are not yet published; however, preliminary data are available in abstracts.[19-23] Sensitivity to allergens was confirmed by skin-prick testing and the presence of elevated IgE levels at baseline.[7,8,11] Omalizumab

was administered by intravenous injection in early clinical trials; however, late phase trials have used subcutaneous injection as the route of administration.

Allergic Asthma

Patients with allergic asthma were receiving inhaled or oral corticosteroids prior to enrolment[11,19,20,23] and had moderate (FEV_1 = >60 to <80% predicted) to severe persistent asthma (FEV_1 ≤ 60% predicted) according to criteria issued by the Global Initiative for Asthma.[24] In general, administration was by subcutaneous injection at a dosage of 150 to 300mg every 4 weeks or 225mg to 375mg every 2 weeks depending on bodyweight and baseline IgE titre.[19,20,23,25] Administration was by intravenous injection in one trial at dosages of 2.5 or 5.8 μg/kg of bodyweight/ng of IgE/ml.[11] A number of studies divided the treatment period into 2 phases.[19,20,25] A 16-week stable treatment period was the first phase in which inhaled corticosteroids were maintained at a regular dosage. This was followed by a 12-week steroid reduction period in which the dosage of inhaled corticosteroid was reduced to the minimal dosage necessary to maintain adequate control of asthma symptoms.

- Omalizumab reduced the frequency of exacerbations requiring systemic corticosteroid treatment or a doubling in dosage of inhaled corticosteroids in 2 trials.[20,25] Adults or adolescents with inhaled corticosteroid-dependent allergic asthma receiving treatment subcutaneously at a dosage of 150 to 300mg every 4 weeks or 225 to 375mg every 2 weeks (n = 542) experienced significantly fewer exacerbations than placebo recipients (n = 529) during 16 weeks of stable treatment ($p \leq 0.006$) [fig. 2]. Exacerbations were also less frequent in the active treatment groups during a subsequent 12-week corticosteroid reduction period ($p \leq 0.002$) [fig. 2].

- A retrospective pooled analysis of these trials found that 9 placebo recipients (1.7%) experienced a serious asthma exacerbation (defined as requiring

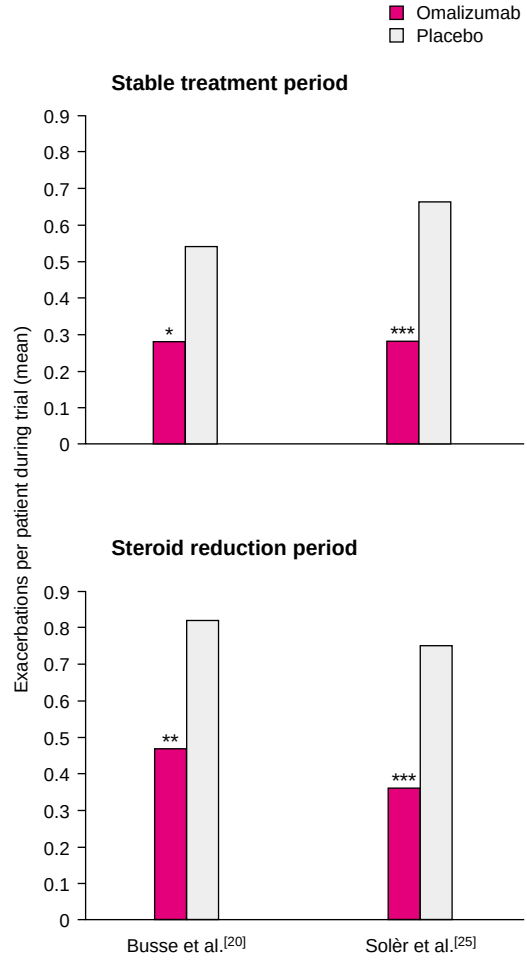


Fig. 2. Reduced number of asthma exacerbations in adults and adolescents treated with omalizumab. Patients with moderate to severe allergic asthma were administered omalizumab 150 to 300mg subcutaneously every 4 weeks or 225 to 375mg every 2 weeks (n = 542) or placebo (n = 529) in 2 multicentre, randomised, double-blind clinical trials.[20,25] Stable treatment with inhaled corticosteroids was maintained for the first 16 weeks of the trial followed by a 12-week steroid reduction period. Exacerbations were defined as worsening asthma requiring systemic corticosteroid treatment or a doubling of the normal dosage of inhaled corticosteroid.
* p = 0.006, ** p = 0.002, *** p < 0.001 *vs* placebo.

in-patient care or hospitalisation, or judged to be life-threatening by the investigator) compared with only 1 omalizumab recipient (0.2%) throughout the 28-week treatment period ($p = 0.01$).[26]

- Patients receiving omalizumab achieved a median 75 and 83% reduction in inhaled corticosteroid dosage in 2 trials during the corticosteroid reduction period,[20,25] which was significantly greater than the 50% reduction obtained in the 2 placebo groups ($p < 0.001$) [baseline corticosteroid dosage = 420 to 1200 μg/day].

- Omalizumab recipients demonstrated statistically greater improvements in quality-of-life scores than patients administered placebo following 16 weeks of stable treatment (0.94 *vs* 0.69 mean change from baseline total score, $p < 0.01$) and also during the 12-week corticosteroid reduction period (0.98 *vs* 0.70, $p < 0.01$).[27] 32.8% of omalizumab recipients had large clinically meaningful improvements (change in score of ≥1.5 points) compared with 17.8% of placebo recipients ($p < 0.01$).

- Omalizumab 150 to 300mg every 4 weeks or 225 to 375mg every 2 weeks was effective in the treatment of allergic asthma in children aged 6 to 12 years over a 28-week period.[19,23] A 100% reduction in the median dosage of inhaled corticosteroids was achieved in the active treatment group, as compared with a 71% reduction in the placebo group ($p = 0.001$) [baseline corticosteroid dosage 168 to 420 μg/day].[19] Clinically and statistically significant improvements from baseline in Paediatric Asthma Quality of Life Questionnaire scores were reported in the active treatment group following 28 weeks of treatment (0.5 *vs* 0.1 units in placebo recipients, $p < 0.05$).[23]

- Intravenous omalizumab 5.8 or 2.5 μg/kg of bodyweight/ng of IgE/ml administered every 2 weeks for 20 weeks improved asthma symptom scores in patients with allergic asthma. Compared with placebo recipients (n = 100), in whom asthma symptom scores improved by 30% after 12 weeks, patients treated with high (n = 103, $p = 0.008$) and low dosage omalizumab (n = 103, $p = 0.005$) had improvements of 42 and 40%, respectively.

- There was a significant increase in mean morning peak expiratory flow rate (PEFR) in the high dosage group (30.7 *vs* 11.3 L/min in the placebo group; $p = 0.007$); however no significant differences were seen between the mean FEV_1 in patients treated with omalizumab or placebo at the end of the 12 weeks.

- Significantly fewer patients experienced asthma exacerbations in the high (30%, $p = 0.03$) and low dosage groups (28%, $p = 0.01$) than in the placebo group (45%) during the entire 20-week period of the trial.

Allergic Rhinitis

The efficacy of omalizumab in patients with birch pollen- or ragweed-induced seasonal allergic rhinitis was evaluated in multicentre, randomised trials in which treatment was initiated ≤4 weeks prior to the pollen season.[7,8,21,22]

- A preliminary trial using subtherapeutic dosages of omalizumab demonstrated dosage- and baseline-IgE dependent reductions in serum free IgE levels in patients with allergic rhinitis. 181 patients received subcutaneous 0.15 mg/kg or intravenous 0.15 or 0.5 mg/kg dosages of omalizumab (≈10.5 or ≈35mg administered to an average sized adult) initiated 1 month prior to the pollen season, and administered 7 times during the 12-week study.[7] The number of patients with IgE levels below the detection limit was too small to demonstrate significant differences in clinical efficacy.

- Worsening nasal symptoms were prevented in patients treated with 2 or 3 subcutaneous doses of omalizumab 300mg during 8 weeks of treatment for birch pollen-induced allergic rhinitis (mean change in symptom scores –0.01 *vs* +0.20 in placebo recipients, $p < 0.001$).[8] The severity of ocular symptoms was also significantly reduced in the active treatment group (n = 165), as compared with the placebo group (n = 86), in whom ocular symptoms worsened (–0.04 *vs* +0.11, $p = 0.031$). Statis-

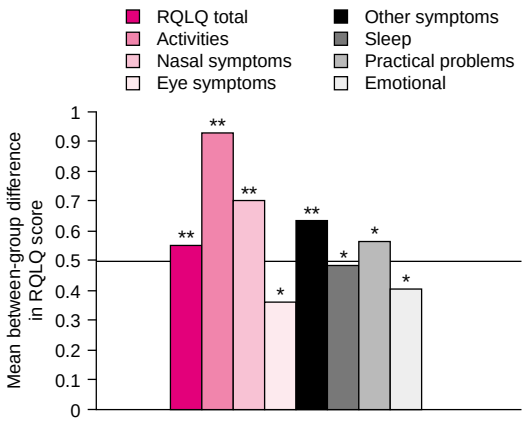


Fig. 3. Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores during treatment with omalizumab. Patients received placebo (n = 86) or subcutaneous omalizumab 300mg (n = 165) every 3 or 4 weeks during an 8-week multicentre, randomised, double-blind, parallel-group study.[8] Differences between RQLQ scores recorded at week 3 or 4 by omalizumab and placebo recipients were calculated. A positive difference denotes a higher mean score recorded by omalizumab recipients. A difference of ≥0.5 units (indicated by horizontal line) is considered to be clinically significant.
* $p < 0.05$, ** $p < 0.001$ omalizumab *vs* placebo.

tically significant differences between placebo and omalizumab recipients were seen in all domains of the Rhinoconjunctivitis-specific Quality of Life Questionnaire (RQLQ), and clinically significant improvements were reported in 4 of the 7 domains and in the total RQLQ score (fig. 3).

- Antihistamine treatment was required on fewer days in patients treated with omalizumab during the 8-week study (28 *vs* 49% in placebo, $p < 0.001$).

- Subcutaneous omalizumab 150 or 300mg given every 3 or 4 weeks was effective in the treatment of ragweed-induced seasonal allergic rhinitis in 2 large, randomised, double-blind, multicentre trials (preliminary data available in abstract form only).[21,22] Omalizumab-treated patients had improvements in total RQLQ scores of 0.42 and 0.43 (150mg and 300mg, respectively) compared with placebo recipients after 12 weeks of treatment ($p \leq 0.025$).[21] Nasal and ocular symptom scores were significantly reduced in the group receiving omalizumab ($p \leq 0.012$) and the average number of antihistamine tablets required per day was approximately half that needed by placebo recipients throughout the pollen season (≤0.20 *vs* 0.37, $p \leq 0.012$).[22]

4. Tolerability

- Omalizumab was well tolerated by adults and children with allergic asthma or seasonal allergic rhinitis during clinical trials.[7,8,11,20,22] Adverse events in patients treated with subcutaneous omalizumab occurred at a similar frequency to those in placebo recipients with the respiratory and nervous systems most frequently affected (usually as a result of upper respiratory tract infections or headaches) [fig. 4].[28]

- Mild to moderate urticaria was reported in patients with allergic asthma and seasonal allergic rhinitis receiving omalizumab treatment during clinical trials.[8,11,12,22] Data from 2 trials in patients with seasonal allergic rhinitis reported the development of urticaria in ≈0.5% of patients after administration of subcutaneous omalizumab.[8,22]

- Two patients (0.5%) discontinued treatment following the development of erythematous rash, facial erythema and eye swelling in a trial in patients with seasonal allergic rhinitis. Patients had received omalizumab treatment during the previous pollen season and were administered omalizumab 4 or 5 times during the subsequent season.[29] Overall, readministration of omalizumab was well tolerated.

5. Omalizumab: Current Status

Omalizumab is a recombinant humanised monoclonal antibody that is currently being reviewed for registration in many countries. Trials to date have demonstrated clinical efficacy in the treatment of allergic asthma and seasonal allergic rhinitis. Omalizumab was well tolerated by patients, adverse

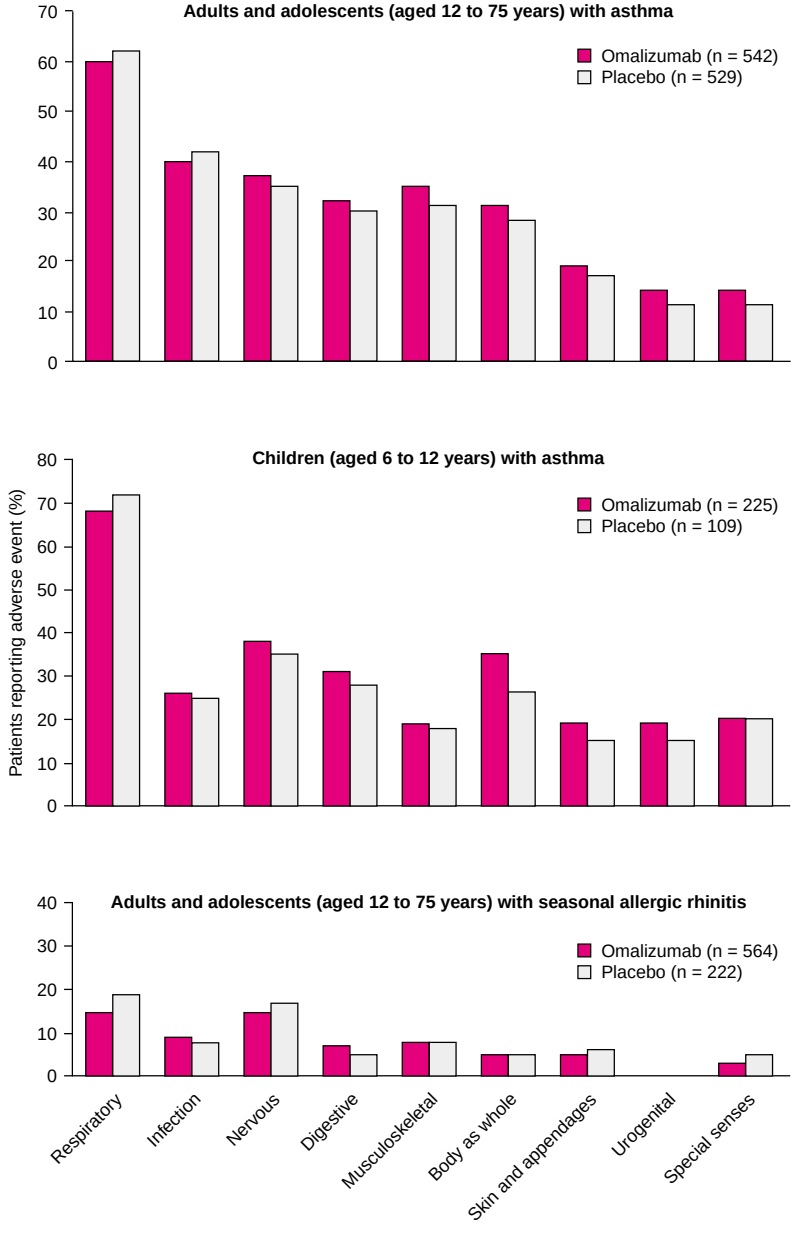


Fig. 4. Percentage of patients reporting adverse events after subcutaneous administration of omalizumab. Pooled data from large randomised, placebo-controlled clinical trials in which omalizumab was administered at dosages of 300mg every 3 or 4 weeks to patients with seasonal allergic rhinitis and at dosages of 150 to 375mg every 2 or 4 weeks to patients with allergic asthma.[28]

events occurred infrequently and were usually mild.

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Correspondence: *Stephanie Easthope,* Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz