EXECUTIVE SUMMARY
In March 2014, the FDA approved the use of omalizumab for the treatment of chronic idiopathic urticaria (CIU) in adults and adolescents who remain symptomatic despite treatment with H1 antihistamines. Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that binds to human immunoglobulin E (IgE) and reduces free IgE. The mechanism for improving symptoms of CIU is unknown.

Efficacy
- There have been five randomized, double blind, placebo-controlled trials evaluating the efficacy and safety of omalizumab in patients with CIU/CSU who continue to be symptomatic despite treatment with usual doses of H1-antihistamines (H1AH). In one trial, patients were receiving up to 4 times the approved H1AH dose in addition to a H2-blocking agent, leukotriene receptor antagonist or both with an inadequate response.
- The trials included patients aged 18-75 years (12-75 years in the U.S.) with moderate to severe symptoms of urticaria during the run-in phase of treatment and prior to randomization.
- Four of the five studies examined doses ranging from 75-600 mg given subcutaneously every 4 weeks as a single dose or up to six doses (24 weeks) followed by a 16-week observation period. In the fifth study, only the 300 mg dose was studied.
- Outcomes examined included urticaria activity score (UAS) at daily or weekly intervals, itch severity score (ISS) and number and size of wheals at daily or weekly intervals, number of angioedema free days, health related quality of life using tools that were specific to dermatologic conditions (see page 3 for description of QOL questionnaires), safety, etc.
- In general, the 300 mg dose was the most effective and resulted in the most improved outcomes for all outcome measures versus placebo, including quality of life; the 150 mg dose was effective for the primary outcome of reduced mean weekly UAS-7 and most other secondary measures; and the 75 mg dose was not found to be different than placebo for the primary endpoint in two of the four studies. The 600 mg dose, examined in one of the five studies, was not shown to be more effective than the 300 mg dose.
- Response was typically reported after one week with the 300 mg and two weeks with the 150 mg dose. During the follow up phase of each study in which omalizumab was no longer administered, measures of urticaria approached values similar to placebo but did not completely return to baseline suggesting that omalizumab does not appear to alter the disease process.
- At this time, there are no clinical trials comparing omalizumab to other step 3 or step 4 therapies (see pages 6-7), including cyclosporine. Therefore, the comparative effectiveness of omalizumab in comparison to other agents used for more difficult to manage patients with urticaria is unknown.

Safety
- Boxed warning regarding the risk of anaphylaxis beginning as early as occurring after the first dose but also has been reported with treatment beyond one year. Patients should be monitored an appropriate amount of time after administration of omalizumab. Medication guides are given to patients with each subcutaneous injection.
- Healthcare providers should be prepared to manage life-threatening anaphylaxis.
- A five-year observational study conducted in patients with moderate to severe persistent asthma did not identify an increased risk of malignancy in omalizumab treated patients versus those not treated. Based upon the limitations of the data, the FDA stated that they were unable to conclude that a higher risk of malignancy does not exist with omalizumab treatment. Additionally, there...
was a higher rate of cardiovascular and cerebrovascular events in patients treated with omalizumab versus those not treated in the same study. However, the magnitude of the risk could not be quantified due to limitations of the observational study including the study design (observational), differences in baseline CV risk and high study withdrawal rate (44%) among other uncontrolled and unmeasured factors.

- Other adverse events include injection site reactions, reported more often in the 300 mg group (2.7% 300 mg, 0.6% 150 mg and 0.8% placebo); fever, arthralgia and rash as part of a constellation of symptoms similar to serum sickness; eosinophilic conditions; severe thrombocytopenia; and hair loss.

**Potential Impact**

- The use of omalizumab in the management of chronic urticaria is recognized as step 3 or step 4 of therapy in guidelines from two professional organizations (pages 6-7). Unfortunately, there is no uniformly accepted preferred treatment between omalizumab and anti-inflammatory or immunosuppressant agents. However, clinical trial evidence is insufficient or lacking for most of the alternative agents including dapsone, sulfasalazine, hydroxychloroquine, tacrolimus or sirolimus, methotrexate, etc. where the evidence is mostly from case series. However, indirect clinical trial data are available to support a similar response rate between cyclosporine and omalizumab and time to response is generally observed within a week for both agents (omalizumab 300 mg). Monitoring of blood pressure and renal function is recommended in patients receiving cyclosporine.

- Omalizumab dose is 150 to 300 mg given subcutaneously every four weeks. The optimal duration of therapy is unknown.

- Since there are no trials directly comparing omalizumab with other agents used in patients with chronic urticaria, the comparative effectiveness or safety between treatments is unknown.

**INTRODUCTION**

Urticaria presents with wheals, angioedema or both and is classified according to whether the symptoms occur spontaneously or are induced in response to a particular trigger. Urticaria is further classified as acute or chronic based upon the duration of symptoms. Acute urticaria is defined as wheals and/or angioedema occurring on most days of the week and lasting less than six weeks while chronic urticaria lasts six weeks or longer. Symptoms arise from the release of histamine and other inflammatory mediators from activated mast cells of the skin. The presence of wheals is generally short-lived, is associated with pruritis and disappears completely within one to twenty-four hours. Angioedema can be associated with more pain than pruritis and resolves within 72 hours. Since wheals and/or angioedema can occur with other medical conditions, the diagnosis of urticaria needs to be differentiated from other potential diagnoses that can present with similar symptoms.1-4

Although chronic idiopathic urticaria (CIU) or chronic spontaneous urticaria (CSU) is not a life-threatening condition, symptoms can negatively impact sleep, work and school activities, social interactions and quality of life.5-7 In some patients with CIU or CSI, symptoms of the disease may be aggravated by certain triggers including nonsteroidal anti-inflammatory drugs (NSAIDs), stress, physical factors (e.g., heat) and changes in dietary habits or alcohol intake.8 However, these triggers are not the main cause for the urticaria in these patients. The cause of chronic urticaria is unknown in more than 80% of affected individuals and symptoms last an average of two to five years.9 The prevalence of chronic urticaria is estimated at 1% of the U.S. population and is more common in women with onset typically occurring between the third and fifth decade of life.10

This review will focus on evidence for the use of omalizumab in the treatment of chronic idiopathic urticaria or chronic spontaneous urticaria in which there is not a recognized stimuli or trigger for the symptoms.

**DESCRIPTION**11

In March 2014, the FDA approved the use of omalizumab for the treatment of CIU in adults and adolescents who remain symptomatic despite treatment with H1 antihistamines. Omalizumab is a...
Omalizumab (Xolair)
Chronic Idiopathic/Spontaneous Urticaria

December 2014
Updated version may be found at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx

recombinant DNA-derived humanized IgG1k monoclonal antibody that binds to human immunoglobulin E (IgE) and reduces free IgE. The mechanism for improving symptoms of CIU is unknown.

FDA APPROVED INDICATIONS
- Moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aero antigen and symptoms that are inadequately controlled on inhaled steroids.
- Chronic idiopathic urticaria in adults and adolescents (12 years and older) who remain symptomatic despite H1 antihistamine treatment. Omalizumab is not indicated for treatment of other allergic conditions or other forms of urticaria.

ALTERNATIVE AGENTS/TREATMENTS
Aside from antihistamines and omalizumab, no other treatments are FDA approved for the treatment of patients with CIU/CSU.

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>FORMULARY</th>
<th>NON-FORMULARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsedating antihistamines</td>
<td>Loratadine, cetirizine</td>
<td>Fexofenadine, desloratadine, levoctizine,</td>
</tr>
<tr>
<td>Sedating antihistamines</td>
<td>Diphenhydramine, hydroxyzine, chlorpheniramine, doxepin, etc.</td>
<td></td>
</tr>
<tr>
<td>Histamine-2 receptor antagonists</td>
<td>Famotidine, ranitidine</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Leukotriene receptor antagonists</td>
<td>Montelukast</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Anti-inflammatory agents/Immunosuppressive agents/Other</td>
<td>Dapsone, hydroxychloroquine, sulfasalazine Cyclosporine A, tacrolimus, sirolimus, methotrexate</td>
<td>Omalizumab (other)</td>
</tr>
</tbody>
</table>

SUMMARY OF THE EVIDENCE

Outcome Measures:
Urticaria activity score (UAS)-Composite score based upon patient’s assessment of severity of urticaria symptoms recorded daily. Severity of symptoms rated 0 (none) to 3 (intense), which includes an assessment of the number of wheals and intensity of pruritis. The daily score is a composite of the score for pruritis and for wheals (range 0-6). Weekly UAS score=UAS7

Itch Severity Score (ISS): patient diary rating severity of itch on 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Weekly ISS score=ISS7

Number of wheals or hives: 4-point scale (0=none, 1=1 to 6 hives, 2=7 to 12 hives, 3=>12 hives)

Quality of Life Measures:
- Dermatology Life Quality Index (DLQI)-Assesses 10 items under 6 headings: Symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. Each is graded on a scale of 0-3 with a score ranging from 0-30. A higher score indicates a greater impact on quality of life.
- Skindex-29-Consists of 29 items separated into 3 domains (physical symptoms, social functioning, emotional state) with scores ranging from 0-100. A higher score indicates a greater impact on quality of life.
- Chronic Urticaria Quality of Life Questionnaire (Cu-Q2oL)-Specifically designed for patients with chronic urticaria, consisting of sections pertaining to physical, emotional, social and practical effects of the disease. The German version consists of 23 items divided into the following
Efficacy:
Prior to the availability of published, randomized, controlled clinical trials of omalizumab in CIU/CSU, there were a number of published case series demonstrating a significant benefit of omalizumab in reducing symptoms or complete resolution of symptoms; even in patients who were considered to have more refractory disease.12-15

There have been five randomized, double blind, placebo-controlled trials evaluating the efficacy and safety of omalizumab in patients with CIU/SCU who continue to be symptomatic despite treatment with usual doses of H1-antihistamines.16-20 In one trial, patients were receiving up to 4 times the approved H1AH dose in addition to a H2-blocking agent, leukotriene receptor antagonist or both with an inadequate response.20 The trials included patients aged 18-75 years (12-75 years in the U.S.) with moderate to severe symptoms of urticaria during the run-in phase of treatment and prior to randomization. Four of the five studies examined doses ranging from 75-600 mg given subcutaneously every 4 weeks as a single dose or up to six doses (24 weeks) followed by a 16-week observation period. In the fifth study, only the 300 mg dose was studied. The mean age of patients was early 40’s and nearly 70% of patients were female. Study sample size ranged from 49 to 336 patients. In general, patients were excluded if they had other dermatologic conditions that may interfere with interpretation of study outcomes, had recent use of corticosteroids or other therapies (e.g., cyclosporine, dapsone, hydroxychloroquine, etc.) for treating urticaria, prior use of omalizumab, were pregnant or likely to become pregnant, etc. Outcomes examined included urticaria activity score (UAS) at daily or weekly intervals, itch severity score (ISS) and number and size of wheals at daily or weekly intervals, number of angioedema free days, health related quality of life using tools that were specific to dermatologic conditions (see page 3 for description of QOL questionnaires), safety, etc. In general, the 300 mg dose was the most effective and resulted in the most improved outcomes for all outcome measures versus placebo, including quality of life; the 150 mg dose was effective for the primary outcome of reduced mean weekly UAS-7 and most other secondary measures; and the 75 mg dose was not found to be different than placebo for the primary endpoint in two of the four studies.17-18 The 600 mg dose, examined in one of the five studies, was not shown to be more effective than the 300 mg dose.17 Response was typically reported after one week with the 300 mg and two weeks with the 150 mg dose. During the follow up phase of each study in which omalizumab was no longer administered, measures of urticaria approached values similar to placebo but did not completely return to baseline suggesting that omalizumab does not appear to alter the disease process. (See Table 2 for results of primary outcome and health related quality of life. See Appendix for more detailed results.)

Table 2: Clinical Trials of Omalizumab in the Management of Chronic Idiopathic or Spontaneous Urticaria

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Outcomes (selected)</th>
<th>Results</th>
<th>Safety/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurer16</td>
<td>Primary Endpoint: Reduction in UAS7 at 24 wks from baseline, Difference from P</td>
<td>Primary Endpoint: OMA: 17.8 (Mean baseline: 24.6 reduced to 6.8) P: 7.9 (Mean baseline: 21.1 reduced to 15.5) Difference 9.9, 95% CI 2.7-17.1, p=0.0089</td>
<td>No difference in incidence of ADEs reported, serious or other.</td>
</tr>
<tr>
<td>N=49, 24 wks</td>
<td>OMA 75-375 mg vs. P every 2-4 wks</td>
<td>QoL: DLQL, Skindex-29, Cu-QoL</td>
<td></td>
</tr>
<tr>
<td>Saini17</td>
<td>Primary Endpoint: Reduction in UAS7 at 4 wks from baseline, Difference from P</td>
<td>Primary Endpoint: 75 mg: 2.9 points (p=0.16 vs. placebo) 300 mg: 13 points (p=0.001 vs. placebo)</td>
<td>No difference in ADEs reported, serious or other.</td>
</tr>
<tr>
<td>N=90, single dose 16 wks</td>
<td>OMA 75, 300 or 600 mg</td>
<td>QoL: Quality of life was significantly improved using all 3 measuring tools in the OMA vs. P groups (p&lt;0.01) DLQL: 62.4% vs. 15.3% Skindex: 50% vs. 6.3% Cu-QoL: 53.2% vs. 5.9%</td>
<td></td>
</tr>
</tbody>
</table>
### Omalizumab (Xolair)

**Chronic Idiopathic/Spontaneous Urticaria**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Primary Endpoint</th>
<th>QoL:</th>
<th>Dose</th>
<th>Efficacy</th>
<th>ADEs</th>
</tr>
</thead>
</table>
| **Maurer**<sup>18</sup>  
N=323, 28 wks  
OMA 75, 150 or 300 vs. P  
every 4 wks for 12 wk,  
followed for added 16 wks | | **Reduction from baseline to week 12 in weekly ISS7** | **QoL:** Change from baseline in DLQI | **600 mg:** 7.7 points (p=0.047 vs. placebo) | | **ADEs** were similar across groups. HA was reported more often in OMA 150 group.  
Nine serious ADEs reported, 5 in 300 mg (melanoma in situ, idiopathic urticaria, nephrolithiasis, tonsillectomy and melena), 2 in P (pneumonia and hemorrhoid), 1 each in 75 (angioedema) and 150 mg (angioedema and urticaria).  
No death or anaphylaxis |
| **Saini**<sup>19</sup>  
N=319, 40 wks  
OMA 75, 150 or 300 mg vs. P  
every 4 wks for 24 wks,  
followed for added 16 wks | | **Change from baseline to week 12 in ISS7.** | **QoL:** Change from baseline in DLQI and improvement in Cu-Q2oL | **Primary Endpoint:** (Mean baseline ISS7 was 14 in all groups)  
OMA 75 mg: -5.9, p=0.46  
OMA 150 mg: -8.1, p=0.001  
OMA 300 mg: -9.8, p<0.001  
P: -5.1 | **QoL:** Mean difference between placebo and 150 and 300 mg dose showed a statistically significant difference in DLQI scores vs. placebo.  
LSMD from Placebo: 150 mg -2.5 (p=0.02) and -300 mg -3.8 (P<0.001) | | **-Treatment emergent ADEs** were more common in the OMA vs. P group (57-69% vs. 51%, respectively). HA, arthralgia and injection site reactions were also more common in the treatment groups.  
-ADEs were mostly mild to moderate in severity and appeared to be related to OMA dose.  
-Serious ADEs were infrequent and none were attributed to the study drug/assignment. |

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**December 2014**

*Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [https://vww.cmopnational.va.gov/cmop/PBM/default.aspx](https://vww.cmopnational.va.gov/cmop/PBM/default.aspx)*
### Kaplan\textsuperscript{30}

<table>
<thead>
<tr>
<th>N=336, 40 wks</th>
<th>OMA 300 mg vs. P every 4 wks for 24 wks, followed for added 16 wks</th>
</tr>
</thead>
</table>
| **Primary Endpoint:** Safety study, incidence and severity of ADEs and serious ADEs at 24 weeks. AND Change from baseline in ISS7 at week 12, primary efficacy endpoint. | **Study discontinuation:**

- **OMA:** 11.1%
- **P:** 21.4%

**Treatment discontinuation:**

- **OMA:** 12.3%
- **P:** 25%

Disease progression was the most common reason for study d/c (4.4% vs. 9.5%) and patient/guardian decision to stop study (4 vs. 9.5%) both lower in OMA group.

Most common reasons for treatment d/c were disease progression (4.4% vs. 10.7%) and ADEs (4.8% vs. 7.1%) with idiopathic urticaria being the most common complaint, both higher in the Placebo group.

**Efficacy:** Mean change from baseline in ISS7 score -8.6 OMA vs. -4 P, which was maintained through week 24. (p<0.001)

**QoL:** Improvement in DLQI from baseline

### Receiving dual therapy with H1AH+H2-blockers (55.5%) or triple therapy with H1AH+H2-blockers+LTRAs (26.6%)

Smaller numbers of patients were receiving H1AH+LTR.

In the majority of patients, H1AH were used a 1-2 times the licensed dose (72.6%) and (27.4%) were receiving H1AH at 3-4 times the usual dose.

Incidence and severity of ADEs were similar between OMA and P with no new safety signals arising.

Headache and upper respiratory tract infections were reported more often with OMA and sinus congestion, migraine and idiopathic urticaria were more common with placebo.

No serious ADEs were felt to be caused by study treatment.

No patient was found to have anti-Oma antibodies at week 40.
### Treatment Guidelines (Place in Therapy) 21-22

<table>
<thead>
<tr>
<th>Professional Organization (Date of Guideline)</th>
<th>Recommended Therapies (Steps)</th>
</tr>
</thead>
</table>
| **Dermatology section of the European Academy of Allergy and Clinical Immunology (EAACI), EU-funded network of excellence, Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) (EAACI/GA²LEN/EDF/WAO: 2013 Revision and Update)** 21 | □ Goal of therapy is for complete symptom control  
**Step 1:** Non-sedating antihistamines  
*If symptoms persist after 2 weeks ⇒*  
**Step 2:** Increase non-sedating antihistamine up to 4 times the approved daily dose  
*If symptoms persist 1-4 weeks after dose increase ⇒*  
**Step 3:** Add omalizumab, cyclosporine A or montelukast (not listed in order of preference)  
*Corticosteroids may also be used at any time if deemed necessary by disease exacerbation (Limit to short course, maximum of 10 days)* |
| **Joint Task Force on practice parameters (JTFPP): American Academy of Allergy, Asthma and Immunology (AAAAI), American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology (AAAAI and ACAAI: 2014 Update)** 22 | □ Treatment is aimed at patient’s level of disease severity and prior treatment history  
□ Medications should be examined at each step for patient response and tolerance  
**Step 1:** Non-sedating antihistamines and avoid triggers that may worsen symptoms (e.g., NSAIDs)  
**Step 2:** One or more of the following:  
• Increase dose of antihistamine started in step 1 |
EVALUATION FOR OTHER AGENTS USED IN PATIENTS WITH REFRACTORY URTICARIA

In the two published guidelines above, there does not appear to be a universally accepted preferred single option listed in step 3 or step 4 for patients not having an adequate response to maximal doses of antihistamines. Therefore, therapy of patients with disease refractory to maximal doses of antihistamines should be individualized with the goal of reducing symptoms of urticaria to satisfy the individual patient and improve quality of life. Although urticaria can be disabling, it does not cause organ damage and is not life-threatening. Therefore, therapies believed to be causing serious adverse events should be discontinued and avoided. As noted previously, urticaria eventually resolves with or without treatment in most patients.

In a section of “Up To Date” concerning the management of refractory chronic urticaria, the authors separate the discussion into whether or not patients are experiencing toxicity from steroids since many of these difficult to control patients have received long courses of corticosteroids. In their discussion, the authors focus on patients without corticosteroid toxicity and suggest a trial of omalizumab or an anti-inflammatory agent (e.g., dapsone, hydroxychloroquine or sulfasalazine) and note that omalizumab is very costly, requires monthly clinic visits for administration and does not appear to influence the disease process or lead to remission. The anti-inflammatory agents are less costly, are taken orally, do not require clinic visits and may be disease modifying. However, they have a slower onset of benefit and may not be as reliably effective. In general, the existing evidence for the anti-inflammatory agents is in the form of case series or observational or unpublished studies and therefore is insufficient or lacking. For patients exhibiting signs of toxicity from steroids, a more efficient approach is necessary and the authors offer the following options: omalizumab or immunosuppressant agents (e.g., cyclosporine A, tacrolimus or sirolimus). The reasons stated for this approach are that these agents act more quickly to reduce symptoms, are more consistently effective and therefore, allow for a quicker reduction in steroid dose or discontinuation of steroids. Existing evidence for the immunosuppressant agents is in the form of case series for tacrolimus or sirolimus but clinical trial evidence does exist for cyclosporine in patients with refractory urticaria and in those patients failing treatment with antihistamines. Time to response is generally a few days with cyclosporine and within a week with 300 mg of omalizumab and two weeks with 150 mg. One author of a review of chronic urticaria commented that only cyclosporine could match the response rate observed with omalizumab treatment using cyclosporine doses ranging from 3-5 mg/kg/day (e.g., 200-300 mg daily). Monitoring of blood pressure and renal function is recommended in patients...
receiving cyclosporine. This same author recommends that if a response to omalizumab is not observed after two subcutaneous injections, reconsider therapy.

At this time, there are no clinical trials comparing omalizumab to other step 3 or step 4 therapies, including cyclosporine. Therefore, the comparative effectiveness of omalizumab in comparison to other agents used for more difficult to manage patients with urticaria is unknown.

SAFETY

Manufacturer Labeling:

Table 3: Adverse Events Occurring in >2% of Patients Treated with Omalizumab and Occurring More Often than in the Placebo Group (Pooled data from trials)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Oma 150 mg (n=175)</th>
<th>Oma 300 mg (n=412)</th>
<th>Placebo (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2 (1.1%)</td>
<td>11 (2.7%)</td>
<td>6 (2.5%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>16 (9.1%)</td>
<td>27 (6.6%)</td>
<td>17 (7%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2 (1.1%)</td>
<td>20 (4.9%)</td>
<td>5 (2.1%)</td>
</tr>
<tr>
<td>URI</td>
<td>2 (1.1%)</td>
<td>14 (3.4%)</td>
<td>5 (2.1%)</td>
</tr>
<tr>
<td>Viral URI</td>
<td>4 (2.3%)</td>
<td>2 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (2.9%)</td>
<td>12 (2.9%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (12%)</td>
<td>25 (6.1%)</td>
<td>7 (2.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (1.1%)</td>
<td>9 (2.2%)</td>
<td>3 (1.2%)</td>
</tr>
</tbody>
</table>

Oma=omalizumab, URI=upper respiratory infection

Other adverse events reported during the 24 weeks treatment and occurring at least 2% or greater and reported for often in the omalizumab group included toothache, fungal infection, urinary tract infection, myalgia, musculoskeletal pain, edema, pyrexia, migraine, sinus headache, anxiety, etc.

Other adverse events include injection site reactions, reported more often in the 300 mg group (2.7% 300 mg, 0.6% 150 mg and 0.8% placebo); fever, arthralgia and rash as part of a constellation of symptoms similar to serum sickness; eosinophilic conditions; severe thrombocytopenia; and hair loss.

Clinical Trials of Chronic Idiopathic/Spontaneous Urticaria:

In clinical trials, generally, the incidence of adverse events was not different between groups receiving omalizumab versus placebo. However, treatment emergent adverse events were greater in the omalizumab group vs. placebo in one study. Most adverse events were considered to be mild to moderate in severity. In the trial by Mauer, et al., there were nine serious adverse events reported; 5 in omalizumab 300 mg, 1 each in the 150 mg and 75 mg omalizumab group and 2 in placebo. The serious events were not considered to be treatment related. Most common adverse events reported in most trials were headache, arthralgia, injection site reactions, upper respiratory infection, migraine, nasopharyngitis, etc. No severe hypersensitivity reactions were reported in the studies of patients with CIU/CSU.

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

**WARNING: ANAPHYLAXIS**

See full prescribing information for complete boxed warning.

Anaphylaxis presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond 1 year after beginning regularly administered treatment. Because of the risk of anaphylaxis, observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening. Inform patients of the signs and symptoms of anaphylaxis and instruct them to seek immediate medical care should symptoms occur.
Contraindications:
Omalizumab is contraindicated in patients with a severe hypersensitivity reaction to omalizumab or any of its ingredients.

Warnings/Precautions: (Selected)
- **Anaphylaxis** has been reported in pre-marketing trials (3/3507 [0.1%] of patients) and in spontaneous post-marketing reports (~0.2% of 57,300 patients treated). Anaphylaxis may occur with the first dose or with subsequent doses (some beyond 1 year of treatment) of omalizumab. Providers experienced in the management of life-threatening anaphylaxis should administer omalizumab in a healthcare setting. Patients should be observed for an appropriate amount of time after omalizumab is administered and told to seek medical care immediately if signs or symptoms of a hypersensitivity reaction occur. Onset of anaphylaxis in the pre-marketing clinical trials was 90 minutes in two patients and two hours in the third patient. In post-marketing reports, onset of anaphylaxis occurred within 30 minutes in 35%, within 30-60 minutes in 16%, within 60-90 minutes in 2%, within 90-120 minutes in 6%, within 2-6 hours in 5%, within 6-12 hours 14% and within 12-24 hours 8%. Onset was unknown in 9% of cases. If a severe hypersensitivity reaction does occur, omalizumab should be discontinued. In 2007, prescribing information was updated to include the boxed warning regarding risk for anaphylaxis in response to spontaneous reports. A medication guide is to be provided to patients with each subcutaneous injection. 23-24
- **Malignancy** has been reported in patients with asthma or other allergic conditions treated with omalizumab (20/4127=0.5% omalizumab vs. 5/2236=0.2% control). However, a five-year post-marketing safety study did not find an increased risk of malignancy in omalizumab treated patients versus those not treated. However, the FDA cites limitations of the five-year study (e.g., observational, high study withdrawal rate [44%], etc.) and therefore cannot rule out the possibility of an increased risk of cancer with omalizumab.11,25
- **Cardiovascular and cerebrovascular events**—A five year, long-term observational study was conducted in patients ≥12 years of age with moderate to severe persistent asthma to determine the long-term safety of omalizumab including the risk of cancer. Although there did not appear to be a higher risk of malignancy in the omalizumab treated versus non-treated groups, there was a higher incidence of overall cardiovascular and cerebrovascular adverse events that were considered serious in the omalizumab treated group (13.4 events/1000 patient years vs. 8.1 control). The following serious events were noted with omalizumab versus control:

<table>
<thead>
<tr>
<th>Event</th>
<th>Omalizumab</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Ischemic Attack</td>
<td>0.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary Embolism/Venous</td>
<td>3.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>2.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Ischemic Stroke/CV Death</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

The magnitude of the risk could not be quantified due to the observational nature of the study, the enrollment of patients with prior exposure to omalizumab, differences in baseline CV risk between groups and the high study withdrawal rate (44%) among other uncontrolled or unmeasured factors.11,25

**DRUG-DRUG INTERACTIONS**
No drug interaction studies have been conducted with omalizumab.

**DOSAGE AND ADMINISTRATION (Chronic Idiopathic Urticaria)**
- 150 to 300 mg subcutaneously every 4 weeks
- The dose of omalizumab is not dependent upon free or total serum IgE or body weight.
• The optimal duration of therapy is unknown and has not been evaluated beyond 24 weeks. Therefore, clinicians are advised to periodically assess the need for continuation of therapy.
• Consult the prescribing information for instructions on preparation and administration of omalizumab.

CONCLUSIONS
The FDA approved the use of omalizumab for the treatment of CIU in adults and adolescents who remain symptomatic despite treatment with H1 antihistamines in March 2014. Omalizumab is a recombinant DNA-derived humanized IgG1k monoclonal antibody that binds to human immunoglobulin E (IgE) and reduces free IgE. The mechanism for improving symptoms of CIU is unknown.

There are five clinical trials reporting a significant reduction in symptoms of chronic urticaria (unresponsive to antihistamines) from baseline with omalizumab 300 mg and 150 mg versus placebo. In each trial, symptoms improved a mean of approximately 70% from baseline. In general, the 300 mg dose was the most effective and resulted in the most improved outcomes for all outcome measures versus placebo, including quality of life; the 150 mg dose was effective for the primary outcome of reduced mean weekly UAS-7 and most other secondary measures; and the 75 mg dose was not found to be different than placebo for the primary endpoint in two of the four studies. The 600 mg dose, examined in one of the five studies, was not shown to be more effective than the 300 mg dose. Response was typically reported after one week with the 300 mg and two weeks with the 150 mg dose. During the follow up phase of each study in which omalizumab was no longer administered, measures of urticaria approached values similar to placebo but did not completely return to baseline suggesting that omalizumab does not appear to alter the disease process.

With regard to safety, there is a boxed warning regarding the risk of anaphylaxis beginning as early as occurring after the first dose but also has been reported with treatment beyond one year. Patients should be monitored an appropriate amount of time after administration of omalizumab. Medication guides are given to patients with each subcutaneous injection. Healthcare providers should be prepared to manage life-threatening anaphylaxis. A five-year observational study conducted in patients with moderate to severe persistent asthma did not identify an increased risk of malignancy in omalizumab treated patients versus those not treated. Based upon the limitations of the data, the FDA stated that they were unable to conclude that a higher risk of malignancy does not exist with omalizumab treatment. Additionally, there was a higher rate of cardiovascular and cerebrovascular events in patients treated with omalizumab versus those not treated in the same study. However, the magnitude of risk could not be quantified because of limitations of the observational study including the study design (observational), differences in baseline CV risk, high study withdrawal rate (44%) among other uncontrolled and unmeasured factors. Other adverse events include injection site reactions, reported more often in the 300 mg group (2.7% 300 mg, 0.6% 150 mg and 0.8% placebo); fever arthralgia and rash as part of a constellation of symptoms similar to serum sickness; eosinophilic conditions; severe thrombocytopenia; and hair loss.

The use of omalizumab in the management of chronic urticaria is recognized in step 3 or step 4 of therapy in guidelines from two professional organizations (pages 6-7). Unfortunately, there is no uniformly accepted preferred treatment between omalizumab and anti-inflammatory or immunosuppressant agents. However, clinical trial evidence is insufficient or lacking for most of the alternative agents including dapsone, sulfasalazine, hydroxychloroquine, tacrolimus or sirolimus, methotrexate, etc. where the evidence is mostly from case series. However, indirect clinical trial data are available to support a similar response rate between cyclosporine and omalizumab and time to response is generally observed within a week for both agents (omalizumab 300 mg). Monitoring of blood pressure and renal function is recommended in patients receiving cyclosporine.

At this time, there are no clinical trials comparing omalizumab to other step 3 or step 4 therapies (see pages 6-7), including cyclosporine. Therefore, the comparative effectiveness of omalizumab in comparison to other agents used for more difficult to manage patients with urticaria is unknown.

REFERENCES

PBM Contact: Cathy Kelley, Pharm.D. [Catherine.kelley@va.gov](mailto:Catherine.kelley@va.gov)
# APPENDIX: Clinical Trials of Omalizumab in Chronic Idiopathic or Spontaneous Urticaria

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Inclusion/Exclusion</th>
<th>Intervention/Outcomes</th>
<th>Results</th>
<th>ADEs/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurer16</td>
<td>Inclusion: Adults 18-70 years with moderate to severe CU with persistent symptoms despite H1AH treatment. (Eligibility was determined by serum IgE &gt;30 IU/mL, specific serum IgE-anti-TPO antibody levels &lt;5 IU/mL and/or weekly UAS score of 10 or &gt;.) Exclusion: acute urticaria, chronic diarrhea, severe renal dysfunction, epilepsy, allergy to antibiotics, or take steroids, MTX, CSA, or other immunosuppressant in 4 weeks before screening.</td>
<td>Intervention: 2-phase screening in which patients were given loratadine 10 mg daily and clemastine as rescue for 1 week. Patients with UAS score &gt;0 for any day during the week were given loratadine 10 mg on demand and up to 3 clemastine per day for 2 weeks. Those patients with UAS weekly score of &gt;10 were randomized to Omalizumab 75 mg-375 mg (Based upon total serum IgE levels and body weight) every 2 to 4 weeks in addition to their background H1AH for 24 weeks.</td>
<td>341 patients screened, 49 randomized (stringent eligibility requirement). 42/49 (85.7%) completed the study. Primary: Reduced UAS7 from baseline after 24 weeks: Oma: 17.8 (Mean baseline: 24.6 reduced to 6.8) Placebo: 7.9 (Mean baseline: 21.1 reduced to 15.5) Difference 9.9, 95% CI 2.7-17.1, p=0.0089 Secondary: Mean UAS AUC: significantly reduced in favor of Oma (p&lt;0.001) The number and intensity of wheals, pruritis, erythema and angioedema were statistically lower in the Oma vs. placebo Complete resolution of wheals occurred in 70.4% Oma vs. 4.5% placebo Concomitant meds significantly reduced from baseline (2.9 loratadine and 6 clemastine 7 days prior to randomization) in Oma at week 24: 0.3 loratadine and 0.7 clemastine vs. 3.3 loratadine and 1.4 clemastine taken during wk 24 (3.5 loratadine and 6.1 clemastine 7 days prior to randomization in placebo) Patient and physician global assessments indicated that 59% and 67% of patients respectively had achieved a complete resolution of symptoms vs. 14% and 4%, respectively for placebo. Quality of life was significantly improved using all 3 measuring tools in the Oma vs. placebo groups (p&lt;0.01) DLQL: 62.4% vs. 15.3% Skindex: 50% vs. 6.3% Cu-Q2oL: 53.2% vs. 5.9% ADEs were reported in 81.5% of Oma and 86.4% of placebo. Most common ADEs were diarrhea, nasopharyngitis and headache. Drug related ADEs were reported in 22.2% of Oma vs. 22.7% placebo (NS) One patient in the placebo group withdrew due to serious ADE (eye infection and angioedema) Study quality rated as good</td>
<td>ADEs were similar across treatment and</td>
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</table>

Saini17
Inclusion: US-12-75 years and Germany 18-
Intervention: Eligible patients (UAS7 12 or >)
90 patients randomized, 90% completed the study.
ADEs were similar across treatment and

December 2014
Updated version may be found at www.pbm.va.gov or https://www.cmopnational.va.gov/cmop/PBM/default.aspx
Omalizumab (Xolair)

**Chronic Idiopathic/Spontaneous Urticaria**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Primary: Reduced UAS7 from baseline, and difference from placebo:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 mg: 2.9 points (p=0.16 vs. placebo)</td>
</tr>
<tr>
<td></td>
<td>300 mg: 13 points (p&lt;0.001 vs. placebo)</td>
</tr>
<tr>
<td></td>
<td>600 mg: 7.7 points (p=0.047 vs. placebo)</td>
</tr>
</tbody>
</table>

**Outcomes:**

**Primary:** Change in weekly UAS score from baseline (UAS7) to week 4.

**Secondary:** Change in weekly UAS score and weekly pruritits score and weekly score for the number of hives from baseline to week 4

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**Maurer**

R. DB, PC, MC, Phase III (N=323) 28 weeks (ASTERIA II)

Dose-ranging study (4 doses given over 12 weeks, each given 4 weeks apart)

Followed for additional 16 weeks after last dose for safety and efficacy

Population mostly women (76%), most were Caucasian (85%) and mean age of 42.5 years.

**Inclusion:** US-12-75 years and Germany 18-75 years with moderate to severe CIU for >3 months with no known cause despite treatment with H1AH at the licensed dose. Allowed AH included: cetirizine 10 mg, levocetirizine 5 mg, fexofenadine 60 mg BID or 180 mg once daily, loratadine 10 mg or desloratadine 5 mg UAS7 12 or > during run-in phase or daily UAS of 4 or >

**Exclusion:** Other skin disease associated with pruritis, prior treatment with Oma, relevant disease that may complicate interpretation of results. The use of other agents for the treatment of CIU was not permitted with the exception of stable H1AH.

**Intervention:** Oma 75 mg, 150 mg or 300 mg or placebo every 4 weeks for 4 doses. Continue H1AH at licensed doses; given diphenhydramine 25 mg to take up to 3 times daily as rescue for itch relief for the study duration. (During 16 week follow up, patients could take one additional H1AH)

**Outcomes:**

**Primary:** Change from baseline to week 12 in weekly ISS. (Baseline ISS7 was 14 in all groups) Oma 75 mg: -5.9, p=0.46 Oma 150 mg: -8.1, p=0.001 Oma 300 mg: -9.8, p=0.001 Placebo: -5.1 After the 12 weeks treatment period, ISS7 increased to values similar to placebo but did not reach baseline during 16 weeks of follow up. This could be explained since patients were permitted to take one additional H1AH during this time.

**Secondary:** Significant differences were noted for both 150 and 300 mg Oma groups vs. placebo in all endpoints assessed except number of angioedema free days and reduction in rescue diphenhydramine which was only significant in the 300 mg group.

466 patients were screened, 323 randomized.

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**December 2014**

*Updated version may be found at [www.pbm.va.gov](http://www.pbm.va.gov) or [https://www.cmopnational.va.gov/cmop/PBM/default.aspx](https://www.cmopnational.va.gov/cmop/PBM/default.aspx)*
### Saini

R, DB, PC, MC  
(N=319)  
40 weeks  
(ASTERIA I)

Dose ranging study  
(treatment given every 4 wks for 24 wks and then followed for 16 weeks)

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Saini | Same as ASTERIA II | Same as ASTERIA II | 319 randomized, 262/319 (82.1%) completed 40 wk study, 265/319 (83.1%) completed 24 wk treatment period.  
Primary: Change from baseline to week 12 in weekly ISS. (Baseline ISS7 was 14 in all groups)  
Oma 75 mg: -6.46, p=0.001  
Oma 150 mg: -6.66, p=0.0012  
Oma 300 mg: -9.4 p<0.0001  
Placebo: -3.63  
Response was noted in 1 week in all groups. MID was reached by 3 wks in 75 mg, 2 wks in 150 and 1 wk in 300 mg.  
Secondary: Significant improvements were noted in all 9 secondary outcome measures for Oma 300 mg, 6 for Oma 150 and only 2 for Oma 75 vs. placebo.  
DLQI showed a significant improvement from baseline in the 300 mg group vs. placebo (p<0.0001)  
After the 24 wk treatment period, outcome measures increased so that they were similar to that seen with placebo. Similar to ASTERIA I, an additional H1AH was permitted to maintain subject in study. |

### Kaplan

R, DB, PC, MC, Phase III  
N=336  
(84 placebo, 252 Oma 300 mg)

24 weeks of treatment with Oma vs. placebo and 16 weeks follow up period.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Intervention</th>
<th>Outcome</th>
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</table>
| Kaplan | Inclusion: US-12-75 years and Germany 18-75 years with moderate to severe CIU with no known cause despite treatment with H1AH at 4-times the licensed dose plus H2-blockers, LTRA or both. Eligible patients had UAS7 scores of 16 or > during 24 weeks of treatment.  
Intervention: Oma 300 mg weekly for 24 weeks or placebo. Continue H1AH up to 4 times licensed dose plus H2-blocker, LTRA or both. Diphenhydramine was permitted up to 3 times daily as rescue. After 24 wk treatment, patients were followed for another 16 weeks.  
480 screened, 336 randomized. 290 (86.3%) completed the study.  
Receiving dual therapy with H1AH+H2-blockers (55.5%) or triple therapy with H1AH+H2-blockers+LTRAs (26.6%) Smaller numbers of patients were receiving  
Incidence and severity of ADEs were similar between Oma and placebo with no new safety signals arising.  
Headache and upper respiratory tract infections were reported more often with Oma and sinus congestion. |
Mean age 43.1 years, 71.9% female.

run-in phase, weekly ISS score of 8 or > and daily physician assessed UAS of 4 or > on one screening day and receiving licensed doses of H1AH

Exclusion: Clear cause for CIU/CSU, immunosuppressive drugs or steroids used within 30 days prior to 14 day run-in phase, history of malignancy, hypersensitivity to Oma, or treatment within past year, evidence of parasitic infection, history of anaphylactic shock pregnancy, etc.

<table>
<thead>
<tr>
<th>Outcomes:</th>
<th>H1AH+LTRA. In the majority of patients, H1AH were used a 1-2 times the licensed dose (72.6%) and (27.4%) were receiving H1AH at 3-4 times the usual dose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary:</td>
<td>Study discontinuation: Oma 11.1%, Placebo 21.4%</td>
</tr>
<tr>
<td></td>
<td>Study discontinuation: Oma 12.3%, Placebo 25%</td>
</tr>
<tr>
<td></td>
<td>Disease progression was the most common reason for study d/c (4.4 vs. 9.5%) and patient/guardian decision to stop study (4 vs. 9.5%) both lower in Oma group.</td>
</tr>
<tr>
<td></td>
<td>Most common reasons for treatment d/c were disease progression (4.4% vs. 10.7%) and ADEs (4.8% vs. 7.1%) with idiopathic urticaria being the most common complaint, both higher in the Placebo group.</td>
</tr>
<tr>
<td>Efficacy:</td>
<td>Mean change from baseline in ISS/7 score was -8.6 Oma vs. -4 placebo, which was maintained through week 24 (p&lt;0.001). Other endpoints were similarly improved with Oma vs. placebo, including HRQoL. Over 50% of patients had a UAS7 score of 6 or &lt; and a third of patients were hive and itch free at 12 weeks.</td>
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</table>

migraine and idiopathic urticaria were more common with placebo.

No serious ADEs were felt to be causes by study treatment.

No patient was found to have anti-Oma antibodies at week 40.

Similar to ASTERIA I and II, symptoms appeared to rise to values observed with placebo after the 24-wk treatment phase, Oma did not appear to alter the disease process.

Study rated as moderate-good quality. Study is limited by small sample size to identify new or rarer ADEs with use of Oma in these patients.

ADEs-adverse events, AUC-area under the curve, CSA-cyclosporine A, CU-chronic urticaria, DLQI-Dermatology Life Quality Index, H1AH-H1 antihistamines, HRQoL=health-related quality of life, ISS=itch severity score, LTRA=leukotriene receptor antagonist, MID-minimally important difference, MTX-methotrexate, Oma-omalizumab, QOL-quality of life, UAS-urticaria activity score