



## THE NEW IDSA RECOMMENDATIONS FOR ACUTE BACTERIAL RHINOSINUSITIS: EMPIRIC ANTIBIOTIC THERAPY IN ADULTS

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**R**hin sinusitis (RS) is a common disease associated with high treatment costs, lost workdays, and significant morbidity.<sup>1</sup> In the United States an estimated 31 million adults suffer from RS and in 2008, nearly 1 in 7 of all non-institutionalized adults over 18 years of age were diagnosed with RS in the previous 12 months.<sup>2,3</sup> The disease results in approximately 3.1 million ambulatory care visits annually in the United States, with the total direct healthcare costs attributed to sinusitis estimated at \$5.5 billion per year.<sup>4,5</sup> The indirect costs of RS includes restricted activity at 73 million days and 5.67 workdays annually missed, similar to that for acute asthma at 5.79 days.<sup>5,6</sup> RS patients were more likely to spend greater than \$500 per year on health care than were patients with hay fever, chronic bronchitis, ulcer disease, and asthma.<sup>6</sup>

### PREVIOUS RECOMMENDATION

The role of antibiotic therapy in ARS has been controversial for some time. Hickner et al. discussed the principles of appropriate antibiotic use in adults with ARS in an article published in 2001.<sup>9</sup> The authors discussed the epidemic increase in antibiotic-resistant *S. pneumoniae* due to excessive antibiotic use. The article promoted the development of ARS educational materials for patients and clinicians, along with the establishment of evidence-based practice guidelines intended

to decrease the inappropriate use of antibiotics for ARS. Following the release of the Hickner et al., several organizations published ABRS treatment guidelines intended to address antibiotic over-prescribing. These organizations include the American College of Physicians (ACP),<sup>9,10</sup> the American Academy of Pediatrics (AAP),<sup>11</sup> the Sinus and Allergy Health Partnership (SAHP),<sup>12</sup> the Joint Council of Allergy, Asthma and Immunology (JCAAI),<sup>13</sup> the Agency for Health Care Research and Quality (AHRQ),<sup>14</sup> the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS),<sup>5,15</sup> the Institute for Clinical Systems Improvement (ICSI),<sup>16</sup> and the Canadian Society of Otolaryngology–Head and Neck Surgery (CSO-HNS).<sup>17</sup> These guidelines offer differing opinions on when to start antibiotic therapy and recommended first-line empiric antibiotic choice (**Table 1**).<sup>3,10-17</sup> Decisions on ABRS empiric antibiotic therapy may differ between practitioners based on which guideline is referenced and may contribute to the prescribing differences seen between practitioners.

Previous recommendations have been unanimous in the use of amoxicillin as initial therapy. Recent guidelines, such as the ICSI guidelines<sup>16</sup> for respiratory illness and the Canadian practice guidelines<sup>17</sup> for ARS continue to recommend amoxicillin as first-line treatment. The change from amoxicillin to amoxicillin-clavulanate in the new 2012 IDSA guidelines is a different approach to initial antibiotic empiric therapy for ABRS in adults.<sup>3</sup>

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**Table 1 | ABRS Guideline Recommendations for Initial Antibiotic Empiric Therapy per Organization**

	ACP <sup>10</sup>	AAP <sup>11</sup>	SAHP <sup>12</sup>	JCAAI <sup>13</sup>	AHRQ <sup>14</sup>	AAO-HNS <sup>15</sup>	ICSI <sup>16</sup>	CSO-HNS <sup>17</sup>	IDSA <sup>3</sup>
Initial Antibiotic	Amox	Amox <sup>‡</sup>	Amox <sup>‡</sup>	Amox	N/A*	Amox	Amox	Amox	Amox-clav
Recommended Dosing	N/A	90 mg/kg/day in 2 divided doses	1.5-4 grams/day	500 mg BID	N/A*	N/A	N/A	N/A	500 mg/125 mg PO tid, or 875 mg/125 mg PO bid
Year Published	2001	2001	2004	2005	2005	2007	2011	2011	2012

\*Meta-analysis; no conclusion made on drug of choice for empiric therapy of ABRS in adults; <sup>‡</sup>Pediatric dosing available only; <sup>‡</sup>Amoxicillin and amoxicillin-clavulanate both recommended as first line; AAO-HNS = American Academy of Otolaryngology–Head and Neck Surgery; AAP = American Academy of Pediatrics; ACP = American College of Physicians; AHRQ = Agency for Health Care Research and Quality; Amox = Amoxicillin; Amox-clav = Amoxicillin-clavulanate; CSO-HNS = Canadian Society of Otolaryngology–Head and Neck Surgery; ICSI = Institute for Clinical Systems Improvement; IDSA = Infectious Disease Society of America; JCAAI = Joint Council of Allergy, Asthma, and Immunology; N/A = Not Available; SAHP = Sinus and Allergy Health Partnership

### RECOMMENDATION: THE EVIDENCE

The 2012 IDSA guideline recommends amoxicillin-clavulanate as first-line antibiotic therapy for adult patients with ABRS, differing from previous guidelines which recommend amoxicillin as the first-line antibiotic. The new recommendation is based on in vitro susceptibility data and the current prevalence rates of b-lactamase production among *H. influenzae*.<sup>3</sup> Prevalence rates of ABRS pathogens in children and adults vary slightly, with *S. pneumoniae* remaining the most prominent pathogen in both populations (**Table 2**). The choice of amoxicillin-clavulanate as first-line therapy was primarily based on national surveillance data from the United States that was gathered in three separate studies: Harrison et al.,<sup>18</sup> Critchley et al.,<sup>19</sup> and Sahm et al.<sup>20</sup> These surveillance studies examined the Clinical and Laboratory Standards Institute (CLSI) susceptibilities and pharmacokinetic/pharmacodynamic (PK/PD) susceptibilities of the most prominent pathogens in ABRS (**Table 3**). CLSI susceptibility breakpoints are tested clinically using broth microdilution, while PK/PD susceptibility breakpoints are calculated from population-based PK studies and compared with minimum inhibitory concentration (MIC) distributions for each targeted pathogen.<sup>18</sup>

Harrison et al. collected pediatric respiratory isolates from patients up to 18 years old between January 2005 to August 2007 from two children’s hospitals in the central United States.<sup>18</sup> Duplicate isolates from the

**Table 2 | Prevalence of Respiratory Pathogens in Patients with ABRS<sup>3</sup>**

Pathogen	Adults	Children
<i>S. pneumoniae</i>	38%	21-33%
<i>H. influenzae</i>	36%	31-32%
<i>M. catarrhalis</i>	16%	8-11%

same patient were not utilized. Isolation and identification of isolates were performed according to the CLSI standard protocols. Control strains used with daily testing for each pathogen were those recommended by the CLSI. Of all the isolates tested, 143 isolates were non-typeable *H. influenzae*, 208 were *S. pneumoniae*, and 62 were *M. catarrhalis*.<sup>18</sup>

Based on CLSI and PK/PD breakpoints, b-lactamase-non-producing non-typeable *H. influenzae* were all susceptible to high-dose amoxicillin and high-dose amoxicillin-clavulanate, while 96% were susceptible to standard-dose amoxicillin. Standard-dose amoxicillin and amoxicillin-clavulanate is defined as 45 mg/kg/day, while high-dose amoxicillin and amoxicillin-clavulanate is defined as 90 mg/kg/day. b-lactamase producing non-typeable *H. influenzae* isolates were 58% susceptible to standard and high-dose amoxicillin, 85% susceptible to standard-dose amoxicillin-clavulanate, and 100% susceptible to high-dose amoxicillin-clavulanate.<sup>18</sup>

Among the *S. pneumoniae* isolates, 89.4% were CLSI susceptible to high dose amoxicillin and 73.5% were PK/PD susceptible to standard dose amoxicillin. Amoxicillin-clavulanate was not tested and a reason for not testing was not provided.<sup>18</sup>

*M. catarrhalis* isolates were tested against amoxicillin, which at the high dose had 4.8% CLSI susceptibility and 11.2% PK/PD susceptibility. At the standard dose of amoxicillin, a 4.8% susceptibility was seen on both susceptibility measures. High dose amoxicillin-clavulanate showed 100% PK/PD isolate susceptibility, while the standard dose amoxicillin-clavulanate showed 88.7% PK/PD isolate susceptibility.<sup>18</sup>

Critchley et al. collected respiratory tract isolates from 104 participating institutions across the United States between October 2005 and April 2006.<sup>19</sup> The isolates were limited to one per patient and were collected from clinical samples derived from various up-

**Table 3 | Comparison of CLSI Susceptibilities Between Surveillance Studies in ABRS**

	Harrison 2009 <sup>18</sup>			Critchley 2007 <sup>19</sup>			Sahm 2007 <sup>20</sup>		
	S. pneumo	H. influ	M. cat	S. pneumo	H. influ	M. cat	S. pneumo	H. influ	M. cat
# of isolates	208	143	62	1543	987	486	4958	907	782
Amox, stand <sup>†</sup>	74%*	58%	5%	N/A	N/A	N/A	92%	N/A	N/A
Amox, high <sup>‡</sup>	89%	58%	5%	N/A	N/A	N/A	N/A	N/A	N/A
Amox-clav, stand <sup>#</sup>	N/A	100%	89%*	92%	100%	N/A	N/A	100%	100%
Amox-clav, high <sup>‡</sup>	N/A	100%	100%*	N/A	N/A	N/A	N/A	N/A	N/A

\*PK/PD susceptibility percentage. No CLSI susceptibility percentage available; Amox, stand = Amoxicillin standard dose; Amox, high = Amoxicillin high dose; Amox-clav, stand = Amoxicillin-clavulanate standard dose; Amox-clav, high = Amoxicillin-clavulanate high dose; H. influ = *Haemophilus influenzae*; M. cat = *Morexella catarrhalis*; N/A = Not Available; S. pneumo = *Streptococcus pneumoniae*

per and lower respiratory tract sites, blood, ears, and eyes. Subject demographic information was also collected. All isolates were subcultured and reidentified by standard methods. A total of 1,543 isolates of *S. pneumoniae* were collected, 69.1% of those originated from respiratory specimens. *H. influenzae* isolates totaled 987, with 89.4% derived from respiratory specimens. A total of 486 *M. catarrhalis* isolates were collected, 95.3% of which were from respiratory specimen sources.<sup>19</sup>

The isolates were tested to determine the susceptibility to amoxicillin-clavulanate and penicillin, but not to amoxicillin. Preparation of antimicrobial susceptibility testing and breakpoint interpretations were conducted in accordance with the CLSI recommendations. Of the 1,543 isolates of *S. pneumoniae*, 62.1% were penicillin susceptible, 21.9% were penicillin intermediate, and 16% were penicillin resistant. For amoxicillin-clavulanate, 92.2% were susceptible. The 978 *H. influenzae* isolates were classified as b-lactamase positive or b-lactamase negative depending on if the isolate produced a b-lactamase. The 270 (27.4%) *H. influenzae* b-lactamase positive isolates showed a 99.4% susceptibility to amoxicillin-clavulanate, while the 717 (72.6%) b-lactamase negative isolates showed 100% susceptibility. Neither amoxicillin nor penicillin was tested against *H. influenzae*. Susceptibility testing was not performed on the 486 *M. catarrhalis* isolates.<sup>19</sup>

Sahm et al. captured the CLSI susceptibilities for specific pathogens during the Tracking Resistance in the United States Today (TRUST) surveillance initiative. During the study, 4958 isolates of *S. pneumoniae* were collected, with 65.4% susceptible to penicillin and 92.6% susceptible to standard dose amoxicillin-clavulanate; amoxicillin was not tested. *H. influenzae* isolates were 100% susceptible to standard dose

amoxicillin-clavulanate; high dose amoxicillin-clavulanate and amoxicillin were not tested. *M. catarrhalis* isolates were 100% susceptible to standard dose amoxicillin-clavulanate, but were not tested using high dose amoxicillin-clavulanate or amoxicillin.<sup>20</sup>

### ANALYSIS OF EVIDENCE BEHIND NEW RECOMMENDATION

The three surveillance studies were not without shortcomings. In the Harrison et al. study,<sup>18</sup> only isolates from children with serious or recurrent infections were tested. The isolates obtained from these children may not accurately reflect the general population, as recent antibiotic use or already present antibiotic resistance may have been present. *S. pneumoniae* susceptibility to amoxicillin-clavulanate was not measured, even though the prevalence of this pathogen is highest among ABRS cases. The authors concluded that amoxicillin should remain the drug of choice for patients with infrequent ABRS.<sup>18</sup>

Critchley et al.<sup>19</sup> failed to provide demographic information such as age, sex, or race, for the *H. influenzae* and *M. catarrhalis* participants. The regions tested were predominately the north and northeast and since antibiotic susceptibility can be regionally dependent, this data may not be representative of the whole nation or applicable to every region. Only susceptibility to *S. pneumoniae* with standard dose amoxicillin-clavulanate was measured and only standard amoxicillin-clavulanate susceptibility was measured for *H. influenzae*, while *M. catarrhalis* was not tested.<sup>19</sup>

Sahm et al.<sup>20</sup> only tested *S. pneumoniae* with standard-dose amoxicillin, *H. influenzae* with only standard-dose amoxicillin-clavulanate, and *M. catarrhalis* with only standard-dose amoxicillin-clavulanate.<sup>20</sup> Their

findings do not offer a direct comparison of amoxicillin to amoxicillin-clavulanate. All three of the studies did not directly compare amoxicillin and amoxicillin-clavulanate susceptibility of *S. pneumoniae* isolates, nor was any comparison made between the two antibiotic susceptibilities of *H. influenzae* and *M. catarrhalis* by Critchley et al.<sup>19</sup> or Sahm et al.<sup>20</sup>

Based on the surveillance studies, the IDSA purposed a change in initial empiric antibiotic therapy from amoxicillin to amoxicillin-clavulanate (**Table 4**). Standard-dose amoxicillin-clavulanate is recommended as first-line, while second-line antibiotic therapy depends on if a b-lactam allergy exists, if risk of resistance is present, if failure of initial therapy has occurred, or if hospitalization for infection is necessary. The strength and quality of evidence for the amoxicillin-clavulanate recommendation was evaluated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.<sup>21</sup> Based on the GRADE system, the amoxicillin-clavulanate recommendation was weak and based on low-quality evidence. This equates to an uncertainty in the estimates of desirable effects, harms, and burden of the recommendation. This implies that alternatives to amoxicillin-clavulanate may be equally reasonable and that further research is required to improve the confidence in estimated desirable effects, harms, and burden of therapy.<sup>3</sup>

One explanation for the growing trend towards amoxicillin-clavulanate as initial empiric therapy is the possible increase in prevalence of penicillin-nonsusceptible (PNS) and multi-drug resistant (MDR) *S. pneumoniae*, as well as b-lactamase-negative ampicillin-resistant *H. influenzae* and *M. catarrhalis*.<sup>19</sup> Regardless of this trend, high-dose amoxicillin is preferred for PNS *S. pneumoniae* when the resistance is due to a mutation in penicillin binding protein 3

(PBP3) and not b-lactamase production.<sup>18</sup> The addition of a b-lactamase inhibitor such as clavulanate cannot overcome the PBP3 mutation whereas high-dose amoxicillin may retain its activity.<sup>18</sup> The prevalence of resistant isolates, such as PNS *S. pneumoniae*, in the United States is currently unknown.<sup>3</sup>

The introduction of conjugated pneumococcal vaccines has impacted resistance patterns affecting the recovery of *S. pneumoniae* and *H. influenzae* isolates from upper respiratory tract samples.<sup>3</sup> The IDSA recommends amoxicillin-clavulanate due to the increasing incidence of disease caused of b-lactamase producing *H. influenzae* (37-50%), but data for this recommendation was extrapolated from children with acute otitis media.<sup>3</sup> When the incidence of offending pathogens in acute maxillary sinusitis were compared before and after the use of the conjugated pneumococcal vaccine the rates of non-type b *H. influenzae* increased from 36% to 43% (p<0.05); however, the change in the incidence of b-lactamase producing non-type b *H. influenzae* was not statistically significant.<sup>23</sup> As non-b-lactamase producing *H. influenzae* would likely remain susceptible to amoxicillin the addition of clavulanate to cover the b-lactamase producing strains of *H. influenzae* may not be needed as the rates of infection with this pathogen do not appear to be changing significantly due to the use of the conjugated pneumococcal vaccine.

As the majority of ARS cases are viral, the overuse of antibiotics may be increasing the prevalence of resistant pathogens.<sup>22</sup> Although culture-directed antibiotics are ideal, empiric antibiotic therapy should be used in the absence of cultures.<sup>7</sup> Resistance patterns in select regions and institutions should also be taken into account. Continued surveillance of antibiotic susceptibility of respiratory pathogens should be performed at the institutional, regional, and national lev-

**Table 4 | IDSA Antibiotic Treatment Guideline of Adults with ABRS<sup>3</sup>**

Indication	First-line (Daily Dose)	Second-line (Daily Dose)
Initial empirical therapy	Amoxicillin-clavulanate (500 mg/125 mg PO tid, or 875 mg/125 mg PO bid)	Amoxicillin-clavulanate (2000 mg/125 mg PO bid) or Doxycycline (100 mg PO bid or 200 mg PO qd)
β-lactam allergy		Doxycycline (100 mg PO bid or 200 mg PO qd) or Levofloxacin (500 mg PO qd) or Moxifloxacin (400 mg PO qd)
Risk for antibiotic resistance or failed initial therapy		Amoxicillin-clavulanate (2000 mg/125 mg PO bid) or Levofloxacin (500 mg PO qd) or Moxifloxacin (400 mg PO qd)
Severe infection requiring hospitalization		Ampicillin-sulbactam (1.5–3 g IV every 6 h) or Levofloxacin (500 mg IV qd) or Moxifloxacin (400 mg IV qd) or Ceftriaxone (1–2 g IV every 12–24 h) or Cefotaxime (2 g IV every 4–6 h)

Abbreviations: bid - twice daily; qd - daily; IV - intravenously; PO - orally; tid - 3 times a day



el.

As the use of amoxicillin-clavulanate continues, cost and adverse effects must be taken into consideration as well as its wide spectrum and antibacterial coverage. Amoxicillin, in comparison, is safe and effective, while having a low cost and narrow microbial spectrum.<sup>24</sup> Ultimately, the goal of ABRs antibiotic therapy is to eradicate the bacterial pathogen, to alleviate symptoms, prevent complications, and aid in recovery. The IDSA decided to recommend amoxicillin-clavulanate due to its improved coverage of both ampicillin-resistant *H. influenzae* and *M. catarrhalis*.<sup>3</sup> Yet the three surveillance studies used by the IDSA for the guideline did not properly compare standard-dose and high-dose amoxicillin and amoxicillin-clavulanate.<sup>18,19,20</sup> The IDSA also did not provide the ampicillin-resistant *H. influenzae* and *M. catarrhalis* prevalence rates that the new recommendation is based upon. After analysis of the new IDSA recommendation, high-dose amoxicillin likely remains a reasonable option for the initial treatment of ABRs.<sup>3</sup> Local susceptibility patterns should be consulted and followed to determine the most appropriate antibiotic specific to the region of practice.

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### SUMMARY

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Rhinosinusitis is a common disease that is predominately caused by viruses, yet the disease accounts for one in five antibiotic prescriptions for adults in the United States. Growing antibiotic resistance trends have caused a shift in the empiric treatment of rhinosinusitis from amoxicillin to amoxicillin-clavulanate. Lack of agreement between treatment guidelines has added additional confusion for the provider and the patient. Based on the GRADE system, supported evidence for this change is weak and of low-quality. Therefore, changes to antibiotic empiric treatment of acute rhinosinusitis should be based on regional and institutional susceptibilities, the prescriber's discretion, and on a case-by-case basis. Amoxicillin may still be the drug of choice for first line empiric therapy in many patients with ABRs.<sup>16,17</sup>

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## TERIFLUNOMIDE: A NEW OPTION IN MULTIPLE SCLEROSIS

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**M**ultiple Sclerosis (MS) is a chronic, debilitating, autoimmune disease of the central nervous system (CNS) that afflicts an estimated 2.1 million people worldwide. In the United States alone, approximately 400,000 people suffer from this unpredictable disease with about 200 new diagnoses every week.<sup>1</sup> MS is associated with a significant burden on patients as well as their families, caretakers, and society as a whole. In 2007, total overall costs were approximately \$50,707 per MS patient per year. These costs included informal care, disease-modifying drugs, professional home care, hospitalizations, other prescriptions, early retirement, and loss of employment.<sup>2</sup>

Not only does MS have a significant financial impact on society, but the ways in which the disease manifests itself are highly variable from patient to patient, often making it very difficult to initially diagnose. MS is most commonly found in Caucasians between the ages of 20 and 50 years old. It is 2-3 times more common in women than in men.<sup>3</sup> There are four different types of MS: relapsing-remitting, secondary-progressive, primary-progressive, and progressive-relapsing. However, 85% of patients are initially diagnosed with the relapsing-remitting form of the disease. This form is characterized by clearly defined exacerbations (relapses), or episodes of acute worsening of neurologic function, followed by partial or complete recovery periods (remissions) that are free of disease progression.<sup>1</sup>

The National Multiple Sclerosis Society recommends that relapsing-remitting MS patients be treated

with an FDA-approved “disease-modifying” drug as soon as possible in order to lessen the frequency and severity of MS attacks, reduce the accumulation of brain lesions, and possibly slow the progression of disability.<sup>1</sup> Currently available disease-modifying prescription drugs include injectable dosage forms such as interferon beta-1a (Avonex® and Rebif®), interferon beta-1b (Betaseron® and Extavia®), glatiramer (Copaxone®); intravenous (IV) infusions such as natalizumab (Tysabri®) and mitoxantrone (Novantrone®); and fingolimod (Gilenya®), the first oral disease-modifying treatment option for relapsing MS.<sup>3,4</sup>

In September 2012, Genzyme Corporation received FDA approval for teriflunomide (Aubagio®), the second once-daily oral disease-modifying therapy indicated for the treatment of adults with relapsing forms of MS.<sup>1,5</sup> This article will discuss teriflunomide’s pharmacology, pharmacokinetics, dosing and administration, as well as the current evidence for its efficacy and safety.

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### PHARMACOLOGY

Teriflunomide, the primary active metabolite of leflunomide (used in the long-term treatment of rheumatoid arthritis), is an immunomodulatory agent with additional anti-inflammatory properties. It selectively, non-competitively, and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, which is involved in the *de novo* pyrimidine synthesis that is necessary for DNA replication in lymphocytes. This inhibition results in reduced activation, proliferation, and function of rapidly dividing peripheral T- and B-lymphocytes in response to the autoantigens that are thought to be especially damaging in MS. Additionally, teriflunomide inhibits the production of immune messenger chemicals by T-cells. These effects lead to a reduced concentration of activated lymphocytes in the CNS, thereby reducing the inflammatory demyelination that occurs in MS. Teriflunomide therapy generally preserves the replication and function of slowly dividing lymphocytes, since these cells utilize exogenous supplies of pyrimidine nucleotides. Overall, this mechanism results in less activated lymphocytes in the CNS, which are largely responsible for the characteristic lesions of MS, without compromising the immune system’s response to infection.<sup>6,7,8</sup>

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### PHARMACOKINETICS

Teriflunomide is an orally administered drug that can be taken without regard to food. Its median half-life is 18-19 days, and it is highly protein bound in the

plasma (>99%). The drug is metabolized hepatically by multiple pathways. It is primarily eliminated unchanged in the bile, but is also excreted via fecal and renal routes (**Table 1**).<sup>8</sup>

## CLINICAL TRIALS

### Phase II Trial

A randomized, placebo-controlled, double-blind, multicenter phase II trial evaluating teriflunomide as add-on therapy to current and "stable-dosed" IFN-beta was published in 2012.<sup>7</sup> A total of 118 patients with relapsing MS were randomized to receive either oral placebo in addition to IFN-beta (Avonex® 30 mcg once weekly intramuscular (IM) injection; Rebif® 22 or 44 mcg 3 times weekly subcutaneous (SC) injection; or Betaseron® 250 mcg every other day SC injection), or once daily oral teriflunomide 7 or 14 mg added to IFN-beta for 24 weeks. After that time, 86 patients who still met eligibility criteria elected to enter a 24-week extension phase where they continued to receive their originally assigned treatment regimen, which results in a total of 48 weeks of drug exposure. The primary objective was to evaluate the safety and tolerability of teriflunomide compared to placebo, measured by the treatment-emergent adverse events (TEAEs) that occurred with treatment. The secondary endpoints of the study were MRI activity, specifically a reduction in number of lesions as well as lesion volume, and MS relapses, defined as the appearance of a new clinical sign or symptom or worsening of a previous symptom that persisted for ≥24 hours in the absence of fever.<sup>7</sup>

Across the 3 groups, TEAEs were similar and led to a low incidence of treatment discontinuations. Some of the most common adverse events observed in the teriflunomide treatment groups with a frequency of ≥10% were increased alanine aminotransferase (ALT), decreased lymphocyte count headache, nasopharyngitis,

headache, and diarrhea.<sup>7</sup>

Both teriflunomide groups showed a significant reduction in number of lesions per scan at weeks 24 and 48, with relative risk reductions (RRRs) of 84.6% (P=0.0005) in the 7 mg group, and 82.8% (P<0.0001) in the 14 mg group compared to placebo after 24 weeks. Total lesion volume was also significantly reduced in the 14 mg group with RRR 70.6% (P=0.0154) at 48 weeks, and RRR 64.7% (P=0.0072) at 24 weeks compared to placebo.<sup>7</sup>

Authors concluded that teriflunomide has an "acceptable safety and tolerability and reduced MRI disease activity" when combined with IFN-beta compared to IFN-beta alone.<sup>7</sup>

### TEMSO

The Teriflunomide Multiple Sclerosis Oral (TEMSO) trial, sponsored by Sanofi-Aventis, was a randomized, double-blind, placebo-controlled, parallel-group, phase III study that evaluated the efficacy and safety of teriflunomide in 1,086 (modified intention-to-treat) patients with relapsing MS.<sup>9</sup> Eligible patients were 18 to 55 years of age, met the McDonald criteria for diagnosis of MS, and had a relapsing clinical course with or without disease progression. They were required to have a score of 5.5 or lower on the Expanded Disability Status Scale (EDSS; ranges from 0 to 10, higher scores indicate greater disability) and at least two clinical relapses in the previous two years or one relapse during the preceding year, but no relapses in the 60 days before randomization. Excluded patients had other systemic diseases, were pregnant, or planning to become pregnant during the trial period. After the screening process was complete, eligible patients underwent randomization (stratified according to baseline EDSS score of ≤3.5 or >3.5 as well as by trial site) to receive a once-daily dose of one of the following for 108 weeks: placebo, teriflunomide 7 mg, or

**Table 1 | Pharmacokinetic Profile of Teriflunomide**<sup>8</sup>

<b>Absorption</b>	Time to Cmax: 1-4 hrs; Time to steady state: 3 months; Effect of food: none
<b>Distribution</b>	Plasma protein binding: >99%; Vd: 11 L
<b>Metabolism</b>	Primary: Hydrolysis; Oxidation (minor pathway); secondary: Oxidation, N-acetylation, and sulfate conjugation
<b>Elimination</b>	T <sub>1/2</sub> : 18-19 days; total body clearance: 30.5 mL/hr Bile (primary route): unchanged Fecal: 37.5%; renal: 22.6%
<b>Special Populations</b>	Elderly: Clinical studies did not include patients over 65 yrs of age Pediatrics: Safety and effectiveness not established; use in patients less than 18 yrs of age is not recommended Pregnancy: Category X Renal Impairment: No dose adjustment Hepatic Impairment: Use is contraindicated in severe hepatic impairment (Child Pugh Class C); no dose adjustment for mild-moderate hepatic impairment (Child Pugh Class A-B)

Cmax = peak plasma concentration, hr = hour, L = liters, mL = milliliters, T<sub>1/2</sub> = elimination half-life; Vd = volume of distribution; yrs = years



teriflunomide 14 mg.<sup>9</sup>

The study's primary endpoint was the efficacy of teriflunomide in reducing the annualized relapse rate. A relapse was defined as the appearance of a new clinical sign or symptom, or worsening of a pre-existing sign or symptom that had previously been stable for at least 30 days and that persisted for a minimum of 24 hours in the absence of a fever. The key secondary endpoint was teriflunomide's efficacy in delaying progression of disability over the study period, based on pre-determined changes in the EDSS score. Other secondary endpoints included total lesion volume, number of gadolinium-enhancing lesions on T<sub>1</sub>-weighted images, volume of hypointense lesion components on T<sub>1</sub>-weighted images, number of active lesions, brain atrophy, and patient-reported fatigue.<sup>9</sup>

After 108 weeks, the annualized relapse rate (ARR) for teriflunomide was 37% for both the 7 mg and 14 mg doses, and the ARR for placebo was 54%, translating to a 31% reduction ( $P < 0.001$ ). Estimated proportions of patients who had confirmed disability progression sustained for at least 12 weeks were 27.3% for placebo, 21.7% for teriflunomide 7 mg, and 20.2% for teriflunomide 14 mg. This corresponded to relative risk reductions of 23.7% for lower-dose teriflunomide ( $P = 0.08$ ) and a statistically significant 29.8% for higher-dose teriflunomide ( $P = 0.03$ ), which suggests a possible dose-dependent effect for this endpoint. Both doses improved several MRI measures of disease activity compared to placebo, indicating suppression of active inflammatory lesions. Additionally, compared to placebo, the 7 mg dose resulted in a 39.4% reduction in brain lesion volume on MRI ( $P = 0.03$ ), and the 14 mg dose resulted in a 67.4% reduction ( $P < 0.001$ ). The study showed that patients in the teriflunomide groups also had significantly fewer gadolinium-enhancing lesions per T<sub>1</sub>-weighted scan compared to placebo ( $P < 0.001$  for both doses) as well as fewer unique active lesions per scan ( $P < 0.001$  in both teriflunomide dose comparisons to placebo). However, changes in brain atrophy from baseline along with changes from baseline in fatigue did not differ significantly among the three study groups. The TEMSO trial concluded that once-daily oral teriflunomide treatment provided sustained benefits for patients with relapsing MS, and, therefore is regarded as an effective new monotherapy option for this indication. The authors reported that a potential limitation to this trial was its duration of 108 weeks. Long-term effects or rare adverse events potentially caused by teriflunomide will have to be evaluated in future trials with larger populations and over longer periods of time. Safety experience of teriflunomide can, however, be supplemented by many years of long-term clinical

experience with its prodrug, leflunomide, in patients with rheumatoid arthritis.<sup>9</sup>

After the TEMSO trial was completed, a subgroup analysis was performed in order to report the effects of teriflunomide on annualized relapse rate and disability progression in pre-specified subgroups. Subgroups were stratified based on gender, geographical region, baseline demographics, clinical disease characteristics, relapses in the past two years, MS sub-type, MRI characteristics, total lesion volume, and previous use of disease-modifying MS drugs. The positive effects of teriflunomide were consistent across all subgroups in the TEMSO trial.<sup>10</sup>

### TOWER

The Teriflunomide Oral in People with Relapsing Multiple Sclerosis (TOWER) trial was a phase III, randomized, double-blind, multi-center, parallel group, placebo-controlled study that was completed, but has ongoing data analysis.<sup>11</sup> This trial compared once daily teriflunomide 7 mg or 14 mg against placebo. The study enrolled 1,169 patients with relapsing MS across 26 countries and followed them for a period between 48 and 173 weeks. The average exposure to teriflunomide was 72 weeks. The primary endpoint was annualized relapse rate, which was the number of confirmed relapses per patient-year. The key secondary endpoint was time to disability progression confirmed for a minimum of 12 weeks.<sup>11</sup>

Results of the TOWER study were released via a Genzyme press release in October, 2012. At the end of the trial period, the ARR for the 14 mg dose of teriflunomide was 31.9% compared to placebo (ARR=50.1%), showing a 36.3% reduction ( $P = 0.0001$ ). Additionally, 54% of patients treated with this dose were also relapse-free during the study, compared to 38% on placebo, which correlates to a 37% risk reduction ( $P < 0.0001$ ). A 31.5% risk reduction in 12-week sustained disability progression was also observed in the 14 mg dose compared to placebo ( $P = 0.0442$ ). In patients treated with the 7 mg dose, a 22.3% reduction in annualized relapse rate (ARR=0.0389) was found compared to placebo ( $P = 0.189$ ), and 55% of patients were relapse-free compared to placebo ( $P = 0.0016$ ). Contrary to the significant disability progression reduction found in the 14 mg dose arm, there was no statistically significant difference between teriflunomide 7 mg and placebo for the risk of 12-week sustained accumulation of disability. Adverse events were similar to those in previous studies of teriflunomide in MS. The most common adverse events reported were headache, ALT elevations, hair thinning, diarrhea, nausea, and neutropenia. Specific data regarding the incidence of these adverse events has not yet been re-



leased to the public.<sup>11</sup> These findings are consistent with data found by the TEMSO study<sup>9</sup>, making teriflunomide the first and only oral MS therapy that has significantly slowed the progression of disability in two phase III trials.<sup>11</sup>

## ADVERSE EVENTS

During clinical trials, there were similar proportions of patients in the placebo, lower-dose teriflunomide (7 mg), and higher-dose teriflunomide (14 mg) groups who experienced adverse events (87.5%, 89.1%, and 90.8%, respectively, in the TEMSO trial<sup>9</sup>). Some of the most common adverse events (crude incidence  $\geq 10\%$ ) that also showed increased incidence in the teriflunomide arms and a clear dose-dependent effect included diarrhea; elevated ALT levels; nausea; and hair thinning (**Table 2**). These events rarely led to discontinuation of the study medications, and no deaths were reported.<sup>9</sup>

The following serious adverse reactions were also reported during teriflunomide therapy: hepatotoxicity, bone marrow effects, immunosuppression, infections, peripheral neuropathy, acute renal failure, hyperkalemia, serious skin reactions, blood pressure effects, and respiratory effects.<sup>8,9,11</sup>

In addition to these reported adverse events, teriflunomide also has two black box warnings. Severe liver injury, including fatal liver failure, has been reported in patients taking leflunomide, a drug used in the treatment of rheumatoid arthritis. Since teriflunomide is the active metabolite of leflunomide, and recommended doses of both drugs result in a similar

range of plasma concentrations of teriflunomide, a similar risk is expected with teriflunomide. Therefore, teriflunomide is contraindicated in patients with severe hepatic impairment.<sup>8</sup> Patients with pre-existing liver disease or who are using other potentially hepatotoxic drugs concomitantly with teriflunomide may be at an increased risk of developing elevated serum transaminases. If drug-induced liver injury is suspected, discontinue teriflunomide immediately, and start an accelerated elimination procedure.<sup>8</sup>

The second black box warning indicates high risk of teratogenicity.<sup>8</sup> Based on animal data, teriflunomide may cause major birth defects when used during pregnancy, and is therefore contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during teriflunomide treatment and before completion of an accelerated elimination procedure after treatment is discontinued. Teriflunomide is also detected in human semen, but animal studies to evaluate the risk of male-mediated fetal toxicity have not yet been conducted. Men taking teriflunomide, who do not wish to father a child, must use a reliable form of contraception as well as their female partners. Men wishing to father a child should discontinue teriflunomide therapy and undergo an accelerated elimination procedure to minimize possible risk to the fetus.<sup>8</sup>

Teriflunomide is eliminated very slowly from the plasma and takes an average of 8 months, sometimes up to 2 years, to reach plasma concentrations less than 0.02 mg/L.<sup>8</sup> If a patient decides to discontinue the treatment in order to become pregnant or in case of possible overdose or emerging toxicity, it is recom-

**Table 2 | Most Common Adverse Events in Teriflunomide vs. Placebo<sup>9</sup>**

Adverse Event	Placebo (N = 360); N (%)	TN 7 mg (N = 368); N (%)	TN 14 mg (N = 358); N (%)
Diarrhea	32 (8.9)	54 (14.7)	64 (17.9)
Elevated ALT level	24 (6.7)	44 (12.0)	51 (14.2)
Nausea	26 (7.2)	33 (9.0)	49 (13.7)
Hair thinning or decreased hair density	12 (3.3)	38 (10.3)	47 (13.1)
Nasopharyngitis	98 (27.2)	94 (25.5)	93 (26.0)
Headache	64 (17.8)	81 (22.0)	67 (18.7)
Fatigue	51 (14.2)	47 (12.8)	52 (14.5)
Influenza	36 (10.0)	34 (9.2)	43 (12.0)
Back pain	47 (13.1)	39 (10.6)	41 (11.5)
Urinary Tract Infection	35 (9.7)	27 (7.3)	37 (10.3)
Pain in arms or legs	47 (13.1)	26 (7.1)	33 (9.2)

% = percentage of patients, ALT = alanine aminotransferase, mg = milligrams, N = number of patients, TN = teriflunomide

mended that they undergo one of two accelerated elimination procedures. The first option is to administer cholestyramine 8 g (or 4 g, if poorly tolerated) every 8 hours for 11 days. The second option is the administration of 50 g of oral activated charcoal powder every 12 hours for 11 days. Both regimens were shown to produce more than a 98% decrease in teriflunomide plasma concentrations.<sup>8</sup>

## DRUG INTERACTIONS

There are a number of possible drug interactions associated with the use of teriflunomide; however, the clinical impact of many potential interactions has yet to be determined. The coadministration of teriflunomide and leflunomide is contraindicated. Teriflunomide is an active metabolite of leflunomide; therefore, this duplication of therapy should be avoided. *In vivo* data suggest that teriflunomide is a cytochrome P450 (CYP) 2C8 inhibitor, due to an increase in the peak plasma concentration (C<sub>max</sub>) and area under the curve (AUC) of repaglinide following repeated doses of teriflunomide. Patients should be monitored for adverse effects associated with higher exposure to CYP2C8 substrates. Use of warfarin and teriflunomide showed a 25% decrease in peak international normalized ratio (INR) compared to warfarin alone, warranting close monitoring of INR with concurrent use of these medications. Teriflunomide may also increase the effects of oral contraceptives due to increases in the C<sub>max</sub> and AUC of ethinyl estradiol and levonorgestrel. Also, a decrease in C<sub>max</sub> and AUC was noted with concurrent use of teriflunomide and caffeine, suggesting that teriflunomide may also be a weak inducer of CYP1A2. Since some drugs may need to be adjusted as a result of an interaction with teriflunomide, it is important that healthcare professionals are

aware of and monitor for these possible interactions (Table 3).<sup>8</sup>

## DOSAGE, ADMINISTRATION, AND COST

Aubagio® is available as an oral tablet in 7 mg and 14 mg strengths. It is administered once daily, and can be taken with or without food. While the 14 mg dose shows greater effectiveness, the 7 mg dose may be more appropriate for individuals who may be more sensitive to the drug and experience greater side effects.<sup>4</sup> Due to potential adverse effects, significant monitoring and precautions must take place prior to initiation of therapy. Liver function tests, specifically transaminase and bilirubin levels, as well as a complete blood count (CBC) with differential must be obtained within 6 months before starting Aubagio®. Additionally, ALT levels should be monitored at least monthly for 6 months after the start of therapy. Patients should have a tuberculin skin test performed to screen for latent tuberculosis infections. Blood pressure should be checked before beginning treatment and periodically thereafter. Finally, women of childbearing potential must have a pregnancy test prior to treatment initiation, and it must be confirmed that they are using reliable contraception.<sup>8,12</sup>

A one month supply of Aubagio® in the absence of patient insurance currently costs \$4,039, translating into an annual cost of approximately \$48,468, which is consistent with other MS treatment options (Table 4).<sup>13,14</sup>

## SUMMARY

Aubagio® (teriflunomide) is the second oral disease-modifying treatment option to be approved by the FDA for adults with relapsing forms of multiple

**Table 3 | Drug Interactions With Teriflunomide<sup>8</sup>**

Interacting Drug	Effect on Interacting Drug	Recommendation
CYP2C8 substrates (repaglinide, paclitaxel, pioglitazone, rosiglitazone, naproxen)	May have inc exposure due to CYP2C8 inhibition inc repaglinide C <sub>max</sub> (1.7-fold) and AUC (2.4-fold) <i>in vivo</i>	Monitor for higher exposure; clinical impact yet to be determined
Warfarin	25% dec in peak INR observed <i>in vivo</i>	Close INR follow-up and monitoring
Oral contraceptives	Inc mean ethinyl estradiol C <sub>max</sub> (1.58-fold) and AUC (1.54-fold) <i>in vivo</i> Inc mean levonorgestrel C <sub>max</sub> (1.33-fold) and AUC (1.41-fold) <i>in vivo</i>	Use caution when selecting type and dose of oral contraceptives in patients taking teriflunomide.
CYP1A2 substrates (duloxetine, alosetron, theophylline, tizanidine)	Possible dec efficacy due to weak CYP1A2 induction Dec caffeine C <sub>max</sub> (18%) and AUC (55%) <i>in vivo</i>	Monitor for reduction in efficacy; clinical impact yet to be determined

AUC = area under the curve, C<sub>max</sub> = peak plasma concentration, CYP = cytochrome-P450, dec = decreased, inc = increased, NR = international normalized ratio

**Table 4 | Dosing and Retail Price Comparison of Multiple Sclerosis Drugs** <sup>1,13,14</sup>

Brand (Generic Name)	Frequency/Route/Usual Dose	Mean Annual Retail Price (USD)
Avonex® (interferon beta-1a)	Once weekly; IM injection; 30 mcg	\$48,738
Betaseron® (interferon beta-1b)	Every other day; SC injection; 250 mcg	\$50,426
Copaxone® (glatiramer acetate)	Once daily; SC injection; 20 mg (20,000 mcg)	\$53,253
Extavia® (interferon beta-1b)	Every other day; SC injection; 250 mcg	\$45,267
Gilenya® (fingolimod)	Once daily; oral capsule; 0.5 mg (500 mcg)	\$61,545
Novantrone® (mitoxantrone; available as generic)	Four times per year; IV infusion; 140 mg/m <sup>2</sup> (lifetime cumulative dose limit approx. 8-12 doses over 2-3 years)	\$3,478
Rebif® (interferon beta-1a)	Three times weekly; SC injection; 44 mcg	\$46,917
Tysabri® (natalizumab)	Once every four weeks; IV infusion; 300 mg	\$49,533
Aubagio® (teriflunomide)	Once daily; oral tablet; 7 or 14 mg (7,000 or 14,000 mcg)	\$48,468

IM = intramuscular, mcg = micrograms, mg = milligrams, SC = subcutaneous, USD = United States dollar

sclerosis. It is available in 7 mg and 14 mg doses, both of which were found to significantly reduce the annualized relapse rate in MS patients compared to placebo. Additionally, the 14 mg dose was also shown to significantly decrease 12-week sustained disability progression compared to placebo in both the TEMSO and TOWER studies, making Aubagio® the first and only oral MS therapy to significantly slow the progression of disability in two phase III trials. Some of the most common adverse events reported in clinical trials include elevated ALT levels, diarrhea, headache, hair thinning, and nasopharyngitis. Aubagio® also has block box warnings for severe liver injury and high risk of teratogenicity, which mandate that certain monitoring requirements take place prior to initiation of therapy. Once-daily oral administration of Aubagio® will improve ease of use compared to its injectable counterparts, rendering it an effective and attractive new option in the treatment of relapsing MS.

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## CLINICAL TRIAL UPDATE

**Resumption of warfarin following interruption due to gastrointestinal bleeding** – Gastrointestinal bleeding (GIB) during warfarin therapy, although uncommon, can be serious and potentially life-threatening; major bleeding is also a risk factor for future bleeding. Following a GIB event patients must be carefully assessed to determine if the future risk of major bleeding outweighs the potential protective effects against venous thromboembolism. Witt and colleagues aimed to answer this clinical question in patients whom experienced a GIB event related to warfarin therapy.<sup>1</sup>

Using administrative and clinical databases Witt and colleagues retrospectively evaluated patients who experienced a GIB while receiving warfarin; the patients were further classified according to whether warfarin therapy was resumed in the 90 days following the incident GIB event. Outcomes of interest included recurrent GIB, thrombosis (which included stroke, systemic embolism, and venous thromboembolism), and all-cause mortality between those who restarted warfarin compared to those who did not restart.

Analysis of the administrative and clinical databases identified 442 patients with a warfarin-related GIB event. The mean age was 74.2 years but those who restarted were an average of 5.9 years younger ( $p < 0.001$ ). Compared to those who did not restart, those who restarted warfarin were more likely to have an international normalized ratio (INR) goal of  $\geq 3$  ( $p < 0.001$ ) or a prosthetic heart valve ( $p < 0.001$ ), but were less likely to have hypertension or atrial fibrillation ( $p = 0.03$  for both). Aspirin was used by 46.4% of patients at some point in the 90 days preceding their GIB event but use did not differ between groups. Notably the median INR at the time of the GIB event was 3.0 (interquartile range [IQR]: 2.3-4.3) and did not differ between groups.

Following the index GIB event 260 patients (58.8%) resumed warfarin therapy in a median of 4

days (IQR: 2-9 days) while 182 patients (41.2%) did not resume warfarin in the 90 days following their GIB; 41 patients (9.3%) never discontinued warfarin. Restarting warfarin was associated with a lower risk for thrombosis (hazard ratio [HR]: 0.05, 95% confidence interval [CI]: 0.01-0.58) and a lower risk for all-cause mortality (HR: 0.31, 95% CI: 0.15-0.62). Importantly the risk for recurrent GIB was not increased in those who restarted warfarin (HR 1.32, 95% CI: 0.50-3.57).

The results of this retrospective cohort study suggest resuming warfarin therapy following a GIB does not increase the risk for a recurrent GIB but reduces the risk for thrombotic events during 90 days of follow-up. The results should be interpreted cautiously due to the relatively small numbers of events and patients, short duration of follow-up, and retrospective nature of the study design which cannot rule-out confounding or show causality. Despite these potential limitations it appears the benefits of resuming warfarin therapy outweigh the potential risks in patients with a recent GIB.

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***The PharmaNote is Published by:***  
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Group, Departments of Community  
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Pharmacotherapy and Translational  
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