

Clinical Review, Adverse Events

Drug:	Carbamazepine
NDA:	16-608, Tegretol
	20-712, Carbatrol
	21-710, Equetro
Adverse Event:	Stevens-Johnson Syndrome
Reviewer:	Ronald Farkas, MD, PhD
	Medical Reviewer, DNP, ODE I

1. Executive Summary

1.1 Background

Carbamazepine (CBZ) is an anticonvulsant with FDA-approved indications in epilepsy, bipolar disorder and neuropathic pain. CBZ is associated with Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), closely related serious cutaneous adverse drug reactions that can be permanently disabling or fatal. Other anticonvulsants, including phenytoin, phenobarbital, and lamotrigine are also associated with SJS/TEN, as are members of a variety of other drug classes, including nonsteroidal anti-inflammatory drugs and sulfa drugs. The incidence of CBZ-associated SJS/TEN has been considered “extremely rare,” as noted in current U.S. drug labeling. However, recent publications and postmarketing data suggest that CBZ-associated SJS/TEN occurs at a much higher rate in some Asian populations, about 2.5 cases per 1,000 new exposures, and that most of this increased risk is in individuals carrying a specific human leukocyte antigen (HLA) allele, HLA-B*1502. This HLA-B allele is present in about 5- to 20% of many, but not all, Asian populations, and is also present in about 2- to 4% of South Asians/Indians. The allele is also present at a lower frequency, < 1%, in several other ethnic groups around the world (although likely due to distant Asian ancestry). About 10% of U.S. Asians carry HLA-B*1502. HLA-B*1502 is generally not present in the U.S. Caucasian, Hispanic, and mainland Native American populations, but is present at a low frequency, about 0.4%, in some African American and Alaskan native groups.

1.2 Sources of Data and Major Findings

The following are the major data sources and findings in this review:

Published reports

- Y.T. Chen group, Taiwan
 - There appears to be a strikingly high incidence of CBZ-associated SJS/TEN in Taiwan, about 2.5 cases per 1,000 patients newly treated with CBZ. This incidence would be on the order of 10- to 100-fold higher than the incidence in Caucasians.
 - The increased risk in Taiwan is mainly in individuals with a specific gene allele, HLA-B*1502. Of 60 patients with CBZ-associated SJS/TEN, 59 were positive

for HLA-B*1502. In comparison, rate of carriage of this allele in the general Taiwanese population was about 10%.

[Comment: HLA-B*1502 appears not to be a 'general' risk factor for SJS/TEN. In this population allopurinol-associated SJS/TEN is associated instead with HLA-B*5801].

- Possibly 5% of 'Han Chinese' with HLA-B*1502 will develop SJS/TEN on exposure to CBZ.
- RegiSCAR Group, Europe
 - Four of 12 patients with CBZ-associated SJS/TEN in a case series from Europe were of Asian ancestry, and all four were positive for HLA-B*1502.
 - Both the high percentage of Asians (<1% of the European population is Asian), and the fact that all were positive for HLA-B*1502 support the association of HLA-B*1502 and CBZ-associated SJS/TEN in Asians. This finding also suggests that geographic location is not key to the adverse events, and that U.S., Asians are likely also at increased risk of CBZ-associated SJS/TEN.
- Man et al., Hong Kong
 - Four of 4 Hong Kong Chinese patients with CBZ-associated SJS//TEN were positive for HLA-B*1502. In controls, the carrier rate of HLA-B*1502 was 15%
 - There was one case each of SJS/TEN associated with phenytoin and lamotrigine, with both subjects positive for HLA-B*1502.
[Comment: Since 15% of Hong Kong Chinese are positive for HLA-B*1502, the two cases with the other AEDs might have occurred in HLA-B*1502 patients by chance alone].

Post-marketing Adverse Events Reports

- Reports to World Health Organization (WHO)
 - In spontaneous reporting of CBZ-associated SJS/TEN in 12 countries worldwide, the 2 Asian countries in the group had ≈100-fold higher reporting rate for CBZ-associated SJS/TEN than the other, mainly Caucasian countries (note: reporting rate normalized by CBZ use).
- Reports to sponsor (Novartis)
 - In spontaneous reporting of CBZ-associated SJS/TEN in 12 countries worldwide (partially overlapping with WHO group above), cases were increased about 10-fold in Asian countries relative to countries with mainly Caucasian populations. Japan, an Asian country with a low frequency of HLA-B*1502, had a reporting rate between that in the other Asian countries and in countries with mainly Caucasian populations.

1.3 Conclusions

The following are the major conclusions of this review:

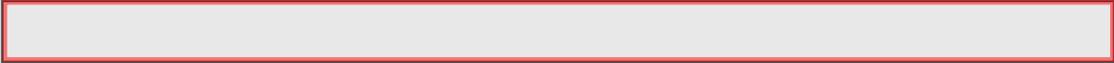
- Asian patients initiating CBZ therapy are at increased risk of developing SJS/TEN, both in absolute terms, and in comparison to Caucasians.

- Independent studies from Taiwan, Hong Kong, and Europe provide consistent evidence that much, if not most of the increased risk of CBZ-associated SJS in Asians occurs in individuals who are genetic carriers of the HLA-B*1502 allele.
- Based on estimates from Taiwan, The risk of SJS/TEN from CBZ in Asian carriers of HLA-B*1502 may be 5%.
- The wide ethnic and geographic origin of Asian patients with CBZ-associated SJS/TEN suggests that U.S. Asians are likely at increased risk. However, no direct data is available quantifying the risk of CBZ-associated SJS/TEN in U.S. Asians.
- Current data does not address the risk of CBZ-associated SJS/TEN in non-Asian carriers of HLA-B*1502, but based on reasonable assumptions the risk may be increased. Of particular concern, in South Asian Indians, the carrier frequency of HLA-B*1502 ranges from between 2% in the majority Hindu population, up to 12% in some tribal minorities.
- In most clinical situations, safe and effective alternative drugs to CBZ could be initiated or continued while the risk of CBZ-induced SJS/TEN was evaluated in patients from at-risk ethnic groups (Asians, including Indians).
- Testing for HLA-B*1502 is widely available from commercial clinical laboratories, and currently is used for tissue transplantation.
- Patients of any ethnic or genetic background who do not develop SJS/TEN after several months of CBZ therapy are at very low risk of the event.

1.4 Recommendations

The following are the major recommendations of this review:

- No change in CBZ therapy is recommended for patients currently tolerating CBZ.
- In patients with ancestry from populations that have a HLA-B*1502 phenotype frequency of 1% or greater, CBZ therapy should not be started unless the patient is tested and found to be negative for the HLA-B*1502 allele [see recommended changes to CBZ labeling, Section 11].
- CBZ labeling should be additionally updated as indicated in Section 11.

- 

2. Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN are characterized by a rapidly developing blistering rash with mucosal involvement. The conditions are closely related, and appear to reflect different severities of the same underlying disease. SJS is defined clinically as epidermal detachment involving less than 10% of total body surface, while TEN involves greater than 30%. Mortality increases with percent epidermal detachment, and is up to $\approx 30\%$ for TEN. Survivors are at particular risk for blindness due to ocular surface damage.

More than 50% of all cases of SJS, and 95% of TEN cases are attributed to medication. Non-medication related cases likely arise secondary to infections, with numerous viral and bacterial agents implicated. The overall incidence of SJS in the U.S. and Europe is about 1- to 6 cases per million person-years, and the overall incidence of TEN is about 0.4 to 1.2 cases per million person-years (Roujeau et al., 1994, *Severe adverse reactions to drugs*. N Engl J Med. 331:1272-85).

More than 100 different drugs have been implicated as causing SJS/TEN. The most commonly implicated drugs are antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiepileptic drugs (AEDs).

In a registry based on an intensive surveying approach in Germany (the authors estimate >90% coverage of cases), the incidence of SJS/TEN related to AEDs was estimated as follows, expressed as risk per 10,000 new users (Mockenhaupt et al., 2005, *Neurology*, 64(7):1134-8):

Carbamazepine (CBZ)	1.4
Lamotrigine (LTG)	2.5*
Phenobarbital (PHB)	8.1
Phenytoin (PHT)	8.3
Valproic acid (VPA)	0.4

*Reviewer note: Lamotrigine is usually associated with a much higher incidence of SJS-like events, about 10/1000 in adults, and 50/10,000 in children. Speculatively, differences in event definition might have led to the much lower numbers reported here. Also, the authors note that direct comparison should not be made between these drugs, as patient populations and indications differed. However, it is difficult to ascribe such an apparent low rate of lamotrigine-associated SJS/TEN to such population differences.

The incidence estimate for CBZ from this Germany study was derived from 39 cases of SJS/TEN identified over a three year period (1998-2001) in 286,360 new CBZ users.

A study in Canada examined serious cutaneous adverse events (events requiring hospitalization) after initiation of phenytoin, carbamazepine, and valproic acid (Tennis and Stern. *Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study*. *Neurology* 1997;49:542–546). The incidence of events was about 10/1000 for phenytoin (half of these were hypersensitivity syndrome) [similar incidence to the German study], and 6/10,000 for CBZ, all 6 representing cutaneous reactions [about 4-fold higher incidence than the German study]. The sample of valproic acid users was small (about 1,500 users, versus almost 10,000 for the other two drugs), with no case of serious cutaneous adverse event.

[Comment: Similar data on CBZ-associated SJS appears to be unavailable for the U.S. The German population may be similar enough to the U.S. Caucasian population that these numbers may represent likely U.S. incidence rates. The U.S. population is about 4 times larger than that of Germany]

In the U.S. about 10- to 20 cases of CBZ-associated SJS/TEN are reported to FDA each year. More than prescriptions for CBZ are filled in the U.S. each year (data from VONA), and U.S. patient exposure was about 1.2 million patient years between 2000 and 2006 (data from Novartis).

SJS/TEN can not be prevented through recognition of early signs or symptoms, although late recognition of SJS/TEN, and continued use of the inciting drug increases mortality by $\approx 30\%$ per day of continued treatment (Garcia-Doval et al., 2000, Toxic epidermal necrolysis and Stevens–Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? Arch Dermatol.136: 323–327).

CBZ and many other drugs associated with SJS/TEN also are associated with less serious rash, including maculopapular eruption (MPE), and the rash often associated with hypersensitivity syndrome (HSS). HSS is also characterized variably by vital organ involvement (e.g. liver, kidney, lung), fever, arthralgia, eosinophilia and lymphadenopathy, in addition to skin rash.

3. Carbamazepine Indications

CBZ is FDA-approved for treatment of epilepsy, mania/bipolar disorder, and neuropathic pain. Alternative FDA-approved therapies other than CBZ are available for these indications, and could potentially be used by patients at high risk of CBZ-associated SJS/TEN.

Epilepsy

Since 1993, eight new AEDs have been approved by FDA (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine zonisamide). In addition, six of the older AEDs continue to be commonly used (Phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, valproate). For any given type of epilepsy, several alternative AEDs are usually treatment options. Selecting an AED based on adverse event profile is common. In patients with a history of drug-induced skin rash, AEDs such as valproate, gabapentin, topiramate, tiagabine, and levetiracetam are thought to carry a lower risk of skin rash and other cross-reactivity.

Mania/Bipolar Disorder

FDA approved drugs for mania/bipolar disorder include lithium, valproic acid, olanzapine, lamotrigine, risperidone, quetiapine, ziprasidone, and aripiprazole. The combination of olanzapine and fluoxetine is also FDA approved. For any given patient, any one of a number of these medications is usually a treatment option.

Neuropathic pain

Medication from several different drug classes are used to treat neuropathic pain, including topical agents, tricyclic antidepressants, anticonvulsants, and nonopioid analgesics. FDA approved drugs for neuropathic pain include CBZ, duloxetine, and pregabalin.

4. Published Reports of Genetic Association

This section of the review examines the scientific content of the published reports supporting a genetic association between CBZ and SJS/TEN in East Asians.

4.1 Taiwan, Y.T. Chen Group

Three publications from this group were reviewed, along with unpublished data presented by Dr. Chen in a seminar at FDA:

- Chung, W.H. et al., *Medical genetics: a marker for Stevens-Johnson syndrome*. Nature. 2004 Apr 1;428(6982):486.
- Hung, S.I. et al., 2006 *Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions*. Pharmacogenet. Genomics. 2006 Apr;16(4):297-306.
- Hung, S.I. et al., 2005 *HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine*. Personalized Medicine. 2005 2(3), 225-237.

Hung et al., 2006, was the group's second paper on the genetic association, on a larger cohort but including all of the patients in the original report of Chung et al., 2004. Hung et al., 2005 presented no new patient data, but reviewed and explained the findings of the first report of the genetic association of CBC-induced SJS/TEN.

The following is derived from the description of studies in both Chung 2004 and Hung 2006.

Study Population:

The study was conducted in Taiwan. Records were reviewed retrospectively for patients admitted to the four different regional hospitals in Taiwan in 1996-2003 with a diagnosis of SJS, TEN or erythema multiforme. The group first reported seventy three total cases of SJS/TEN, with 44 patients agreeing to participate. The group later recruited an additional 15 patients with SJS/TEN.

The SJS/TEN patients were compared to 144 'drug tolerant' subjects selected from patients who had received CBZ for at least 3 months without evidence of adverse reaction (Table 1). These patients were from the neurology clinic of the same regional hospitals where CBZ-SJS patients were recruited. The SJS/TEN patients were additionally compared to 93 unexposed controls randomly selected from a biobank under a nationwide population study. The authors assert that no differences in ethnic background existed among the SJS patients, tolerant controls and normal subjects, and that none of the participants were aboriginal Taiwanese, who account for 2% of Taiwan's population. In Hung 2006, the authors report that two patients were from Hong Kong and one was from the United States. All three of these patients were defined as 'Han Chinese or Chinese descendants,' and had SJS.

[Comment: The biobank sample might differ more from the cases than the tolerant controls, who were from the same clinic as the cases.]

The genetics of patients with CBZ-associated hypersensitivity syndrome (HSS)(N = 13) and maculopapular eruption (MPE)(N = 18) was also studied.

Table 1: Patient Demographics, Taiwan

Table 1 Demographic variables, dosage and duration of carbamazepine (CBZ) exposure, and clinical characteristics in CBZ-induced cutaneous adverse reactions and CBZ-tolerant controls

	Bullous cADRs		Non-bullous cADRs (n=31)	
	SJS/TEN (n=60)	HSS (n=13)	MPE (n=18)	Tolerant controls (n=144)
Sex, n (%)				
Male	33 (55)	9 (69.2)	8 (44.4)	75 (52.1)
Female	27 (45)	4 (30.8)	10 (55.6)	69 (47.9)
Age (years), mean (range)	43.4 (5–80)	51.5 (6–83)	45.9 (7–84)	35.7 (5–79)
CBZ exposure, mean (range)				
Dosage (mg/day)	332.6 (100–600)	420 (300–600)	423.1 (200–800)	793.8 (100–1500)
Duration	15.1 (2–49) days	32.7 (15–54) days	22.4 (7–55) days	75.03 (3–287.5) months
Cutaneous features, n (%)				
Blister or epidermal detachment	60 (100)	0 (0)	0 (0)	Not observed
Mucosal erosions	60 (100)	3 (23)	0 (0)	Not observed
General and laboratory, n (%)				
High fever (>38.5°C)	41 (68.3)	12 (92.3)	11 (61.1)	Not observed
Eosinophil count > 1000/mm ³	4 (6.7)	10 (76.9)	4 (22.2)	Not observed
Atypical lymphocytosis	8 (13.3)	7 (53.8)	3 (16.7)	Not observed
Abnormal liver function	7 (11.7)	11 (84.6)	0 (0)	Not observed
Abnormal renal function	1 (1.7)	2 (15.4)	0 (0)	Not observed

SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema.

SJS/TEN Diagnostic Criteria

Cases were reviewed by two dermatologists who examined photographs, histological data and clinical information.

The authors state that they recruited patients primarily from inpatients who had more severe disease.

SJS was defined as skin detachment of less than 10%, TEN as greater than 30%, and overlapping SJS/TEN as 10-30%. Patients with hypersensitivity syndrome and non-SJS/TEN cutaneous adverse drug reactions (mainly maculopapular rash) were not included.

[Comment: Previous (or subsequent) exposure of patients to other AEDs was not discussed. This information might contribute to understanding of AED cross-sensitivity].

The criteria for HSS in this study were skin rash, plus two of the following symptoms: fever, lymphadenopathy and haematologic abnormalities (e.g. eosinophilia, atypical lymphocytosis) with involvement of at least one internal organ (e.g. hepatitis, pneumonitis, myocarditis, pericarditis, nephritis)

Genotyping

In the first publication (Chung et al., 2004), all HLA-A, -B, -C, and –DrB1 alleles were genotyped, by two different methods (oligonucleotide hybridization and sequencing). In addition, 157 cytochrome P450 SNPs were genotyped by MALDI-TOF mass spectrometry.

In the 2006 publication that included the additional patients, three different, independent genotyping methods in the HLA region were used (STRP markers, SNPs, and HLA genotyping).

Findings:

All but 1 of the 60 SJS/TEN patients was positive for HLA-B*1502. HLA-B*1502 was present in only 4% of tolerant controls.

[Comment: The remaining SJS/TEN patient had a different HLA-B15 variant, HLA-B*1558. HLA-B*15 alleles other than *1502 are common in many populations, and haven't been previously associated with SJS. The biological meaning, if any, of this finding is unknown].

The following are the more detailed findings from each genotyping method. The 3 methods are generally listed in order of increasing specificity:

- STRP Markers
 - HLABC-CA near HLA-B showed the strongest association ($P=3.4 \times 10^{-19}$) [P-values were adjusted using Bonferroni's correction]
- SNPs
 - The rs3130690, an intergenic SNP with 36 kb telomeric to the HLA-B locus demonstrated the strongest association with CBZ-induced SJS/TEN ($P_c=1.29 \times 10^{-39}$). The T allele of the rs3130690 SNP was present in 95% (57/60) of CBZ-SJS/TEN patients, but only in 6.9% (10/144) of tolerant controls [OR=254.6; 95% confidence interval (CI)=70.4–901.9] for TT/TG genotype versus GG genotype).
- HLA genotyping
 - The HLA-B*1502 allele was present in 98.3% (59/60) of CBZ-SJS/TEN patients, whereas only 4.2% (6/144) of the tolerant controls were positive for the allele ($P_c=1.6 \times 10^{-41}$, OR=1357; 95% CI=193.4– 8838.3)

[Comment: Use of multiple genotyping methods suggests that genotyping error can not explain the results].

Several other, much weaker genetic associations were also identified:

- HLA-B*4001 was negatively associated with CBZ-SJS/TEN ($P_c=2.6 \times 10^{-4}$, OR= 0.16; 95% CI=0.1–0.4) (Table 2)

[Comment: This allele was present at higher frequency particularly in MPE subjects (7 of 18, versus 6 of 60 in the SJS/TEN group. Three of 13 subjects with HSS had the allele. It seems difficult to call an allele protective when it might, in fact, be a risk for MPE. The allele doesn't protect against HSS, which is a serious adverse event, and seems to be of limited usefulness clinically)]

- HLA-A*3101 showed an association with MPE/HSS ($P_c=0.0021$). HLA-A*3101 was present in 25.8% (8/31) of patients with MPE/HSS, but only in 2.8% (4/144) of tolerant controls (OR=12.17; 95% CI=3.6–41.2).”(Table 2)

[Comment: HSS is a serious adverse effect. Pre-exposure testing that could avoid HSS might be clinically useful. MPE is a less severe, and more common adverse event, for which pre-exposure testing would be far less useful. Only 2 of 13 subjects with HSS had *3101, suggesting that the allele is a less powerful predictor of the adverse event of greater interest, HSS.]

- Several SNPs in the MHC class II terminal region around the motilin gene showed associations with HSS. The most significant SNP was located in the promoter of this gene, and was associated with increased risk for CBZ induced HSS ($P_c=0.0064$, OR=7.11; 95% CI=3.1–16.5). The allele frequency was 0.46 in cases and 0.11 in tolerant controls.

[Comment: While more data and confirmation is needed, this association with HSS could ultimately be clinically useful.]

Table 2: HLA associations of SJS/TEN, HSS, and MPE

Table 3 Association of HLA alleles with carbamazepine (CBZ)-induced cutaneous adverse reactions

	Tolerant controls ($n=144$)	SJS/TEN ($n=60$)	MPE/HSS ($n=31$)	HSS ($n=13$)	MPE ($n=18$)
HLA-A					
*1101	67	42 [NS; 2.68 (1.4–5.1)]	12 [NS; 0.73 (0.3–1.6)]	6 [NS; 0.99 (0.3–3)]	6 [NS; 0.58 (0.2–1.6)]
*2402	41	5 [0.026; 0.23 (0.1–0.6)]	9 [NS; 1.03 (0.5–2.4)]	3 [NS; 0.75 (0.2–2.7)]	6 [NS; 1.26 (0.5–3.5)]
*3101	4	1 [NS; 0.59 (0.1–4.1)]	8 [0.0021; 12.17 (3.6–41.2)]	2 [NS; 6.36 (1.2–33.9)]	6 [2.2×10^{-3} ; 17.5 (4.6–66.5)]
HLA-B					
*1502	6	59 [1.6×10^{-41} ; 1357 (193.4–8838.3)]	1 [NS; 0.77 (0.1–5.1)]	0 [NS; 0.79 (0.1–8.8)]	1 [NS; 1.35 (0.2–9.3)]
*4001	59	6 [2.6×10^{-4} ; 0.16 (0.1–0.4)]	10 [NS; 0.69 (0.3–1.5)]	3 [NS; 0.43 (0.1–1.5)]	7 [NS; 0.92 (0.4–2.4)]
HLA-Cw					
*0102	54	8 [8.6×10^{-3} ; 0.26 (0.1–0.6)]	14 [NS; 1.4 (0.6–3.0)]	5 [NS; 1.04 (0.3–3.2)]	9 [NS; 1.67 (0.6–4.3)]
*0801	20	56 [7.8×10^{-27} ; 86.8 (29.3–254.6)]	2 [NS; 0.43 (0.1–1.8)]	0 [NS; 0.23 (0–2.3)]	2 [NS; 0.78 (0.2–3.3)]
HLA-DRB1					
*0405	25	1 [0.03; 0.08 (0.01–0.5)]	8 [NS; 1.66 (0.7–4.1)]	1 [NS; 0.40 (0–2.5)]	7 [NS; 3.03 (1.1–8.4)]
*1202	23	41 [2.3×10^{-11} ; 11.4 (5.6–22.9)]	5 [NS; 1.01 (0.4–2.8)]	3 [NS; 1.58 (0.4–5.8)]	2 [NS; 0.66 (0.2–2.8)]

Data are genotype, n of positive subjects [P_c value; odds ratio (95% confidence interval)]. The association of HLA-alleles was examined by Fisher's exact test and the P_c values were adjusted by using Bonferroni's correction for multiple comparisons (17 for HLA-A, 40 for HLA-B, 19 for HLA-C and 30 for HLA-DRB1). NS, Not significant ($P>0.05$). SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis; MPE, maculopapular exanthema; HSS, hypersensitivity syndrome.

Additional analysis of findings presented in Hung et al., 2005

This paper presents an estimate of how a test for HLA-B*1502 might perform in a Taiwanese population (Table 3). The authors state that about 50 new cases of CBZ-associated SJS/TEN per year occur in Taiwan, out of 20,000 new CBZ users.

[Comment: This rate is about 10-fold higher than the rates in Germany and Canada, (reliable U.S. data is not available)]

To calculate the number of exposed patients that are HLA-B*1502 positive, yet don't develop SJS/TEN, the authors multiply 20,000 new users by the 3% frequency of HLA-B*1502 measured in their population of CBZ-tolerant patients. This yields 600 CBZ-tolerant patients.

[Comment: The authors use the 3% allele frequency in their calculation, not the phenotype frequency, which would be close to 6%. The number of CBZ-tolerant HLA-B*1502 patients should therefore be closer to 1,200 out of 20,000].

The authors calculate that the positive predictive value (PPV) for a test based on HLA-B*1502 to predict SJS/TEN susceptible patients would be about 8% ($PPV = \text{true positives}/(\text{true positives} + \text{false positives}) = 50/(50 + 600)$).

[Comment: The authors count as false positives only B*1502 *true positive* patients that are CBZ tolerant. However, B*1502 *negative* patients that are *false positives* due to testing error must also be considered to judge the performance of a real test. If the false positive rate for the test is 1%, then the false positives are closer to $(0.01)(20,000) + 1,200 = 1,400$ [1,200 instead of 600, as explained in the comment above]. The PPV would more realistically be $50/(50 + 1,400) = 3.4\%$.

In a population in which HLA-B*1502 was present at lower frequency, the PPV would be lower. If the HLA-B*1502 allele frequency was 0.5%, the phenotype frequency would be about 1%. In 20,000 new users of CBZ, extrapolating from the Taiwan data, there would be about 8 cases of CBZ-associated SJS. For a test with a false positive rate of 1%, the PPV would be about $8/8 + 400 = 2\%$]

The authors estimate negative predictive value as 100%, based on the fact that in their initial paper all patients with SJS/TEN were, in fact, HLA-B*1502 positive. In the later paper, 1 of 60 patients with CBZ-associated SJS/TEN was HLA-B*1502 negative.

[Comment: The negative predictive value is dominated by the overall rarity of CBZ-associated SJS/TEN, and moreover by the even greater rarity of 'test negative' patients developing CBZ-associated SJS/TEN (about 1 in 20,000). The negative predictive value therefore remains close to 1 regardless of most conditions are other assumptions.]

Table 3: Author-Calculated Test Performance, Taiwanese Population

	CBZ-induced SJS/TEN	CBZ-tolerant
Enrolled no.	n = 50	n = 20,000*
HLA-B*1502-positive no. (%)	50 (100%)	600(3%)
HLA-B*1502-negative no. (%)	0 (0%)	19400(97%)
Fisher's exact test (2-tailed p value)		5.32x10 ⁻⁷⁶
Sensitivity		100%
Specificity		97%
Positive predictive value		7.7%
Negative predictive value		100%
Odds ratio [‡]		3263.03

*Data based on the estimated/observed 50 new SJS/TEN cases per 20,000 new CBZ users each year in Taiwan (0.25% prevalence rate).

4.2 Europe, RegiSCAR Group (J.C. Roujeau senior investigator)

- Lonjou, C., et al., *A marker for Stevens-Johnson syndrome: ethnicity matters.* Pharmacogenomics J. 2006 Jul-Aug;6(4):265-8. Epub 2006 Jan 17.

Study Population:

This paper describes a case series from France and Germany. HLA-B*1502 genotype was determined in twelve patients with CBZ-associated SJS (Table 4). The authors state that ethnicity was assigned based on “skin phenotype” and place of birth of the patient and his/her parents. Four of the twelve patients were of Asian ancestry.

Table 4: RegiSCAR Cases**Table 1 Clinical characteristics of patients with carbamazepine-induced SJS/TEN**

No.	Age	Sex	Phenotype	Diagnosis	%BSA ^a	Mucosa ^b	Place of birth
1	31	M	SJS	Definite	5	2	Vietnam ^c
2	46	M	SJS/TEN overlap	Definite	13	4	Germany
3	52	M	TEN	Definite	90	4	France
4	40	M	SJS/TEN overlap	Definite	26	2	China ^c
5	54	M	SJS	Probable	4	4	France
6	39	F	SJS/TEN overlap	Probable	14	2	Cambodia ^c
7	74	F	SJS/TEN overlap	Definite	17	3	France
8	46	M	SJS	Definite	5	5	Germany
9	57	M	SJS/TEN overlap	Definite	30	2	France
10	42	F	TEN	Definite	70	4	France
11	26	F	SJS	Probable	10	2	Reunion Island ^c
12	37	M	SJS	Probable	6	3	France

^aMaximum of skin detachment (% BSA: body surface area).

^bNumber of mucosal sites involved.

^cPatients with Asian ancestry.

SJS/TEN Diagnostic Criteria

The authors state that a standardized clinical assessment was used, and that each case was reviewed by an expert committee. Only patients with definite or probable CBZ-associated SJS/TEN were included.

Genotyping

Genotyping was conducted by polymerase chain reaction using sequence specific primers (PCR-SSP).

Findings

Four of the 12 patients were positive for HLA-B*1502. All four of these positive patients were of Asian ancestry (1 each from China, Vietnam, Cambodia, Reunion Island). The allele frequency of HLA-B*1502 in these cases was therefore at least 16.7% (4/24 subjects either heterozygote or homozygote positive). The author's cite a study finding that HLA-B*1502 occurs at a frequency of 1-2% in prior studies of European populations [Comment: this estimate seems high, based on public databases]. Based on this proposed background frequency, the author's conclude an increased risk in the European population in carriers of HLA-B*1502.

[Comment: These findings are unlikely given both the low percentage of Asians in France and Germany (<1%) and the minority of Asians expected to be positive for HLA-B*1502 (although varying by population, often about 10%)].

4.3 Hong Kong (Patrick Kwan, corresponding author)

- Man, C.B.L. et al. (2007) *Association between HLA-B*1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese*. *Epilepsia*. 48(5):1015–1018.

Study Population

All patients were from Hong Kong, and were defined by the authors as ‘Hong Kong Han Chinese.’ Cases were patients who developed cutaneous adverse reactions within 8 weeks of starting an AED, and for which no other causes were found. Cases were compared 1:2 to controls. Controls were patients without history of drug-induced cutaneous reactions on the respective AED for at least 3 months. Subjects were identified by database search of patients treated in public hospitals in Hong Kong.

SJS/TEN diagnostic Criteria

SJS was defined as skin detachment of 10% of body-surface area or less, TEN was defined by skin detachment of 30% or more, and intermediate extent was called SJS/TEN overlap. The criteria for HSS were skin rash, plus two of the following features: fever, lymphadenopathy, and hematological abnormalities (e.g., eosinophilia, atypical lymphocytosis) with involvement of at least one internal organ (e.g., hepatitis, pneumonitis, myocarditis, pericarditis, nephritis).

Genotyping

Genotyping was performed using polymerase chain reaction (PCR) with sequence specific primers.

Findings

A total of 24 subjects with cutaneous adverse drug reactions were identified. Of these, 8 had severe cutaneous reactions, 6 SJS/TEN, and 2 HSS. The remaining 16 patients had MPE (Table 5).

Table 5: All Subjects, Chen Study

TABLE 1. Number of subjects in each patient group taking different antiepileptic drugs

Drug	SCR	MPE	Controls
CBZ	4	4	16
LTG	2	4	11
PB	1	0	2
PHT	1	5	13
TPM	–	1	2
VPA	–	2	4
Total	8	16	48

CBZ, carbamazepine; LTG, lamotrigine; MPE, maculopapular exanthema; PB, phenobarbital; PHT, phenytoin; SCR, severe cutaneous reaction; TPM, topiramate; VPA, valproate.

HLA-B*1502 was found in all patients with AED-associated SJS/TEN, but in none with HSS (Table 6). HLA-B*1502 was found in 15% of tolerant controls (OR 3.7-1,400).

Four cases of SJS/TEN were associated with CBZ, and all four were positive for HLA-B*1502. One case each of SJS/TEN was associated with lamotrigine and phenytoin. Both these patients

were positive for HLA-B*1502. The patient taking lamotrigine was taking valproate as background treatment.

There was no difference in the frequency of subjects with the HLA-B*1502 allele between the MPE (12.5%) and control groups (14.5%).

Table 6: Subjects with SJS/TEN or HSS, Chen Study

TABLE 2. Characteristics of patients with severe cutaneous reactions

Patient	Sex	Age ^a (years)	Associating AED ^b	Type of SCR	HLA-B* 1502 allele
1	F	28	CBZ	SJS	Positive
2	M	23	CBZ	SJS	Positive
3	F	53	CBZ	SJS	Positive
4	M	10	CBZ	TEN	Positive
5	F	53	PHT	SJS	Positive
6	F	41	LTG	TEN	Positive
7	M	14	PB	HSS	Negative
8	M	44	LTG	HSS	Negative

AED, antiepileptic drug; CBZ, carbamazepine; HSS, drug hypersensitivity syndrome; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; SCR, severe cutaneous reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

^a Age at development of SCR.

^b An associating AED is one that was commenced within 8 weeks prior to the development of SCR and no other causes were found for the SCR.

[Comment: The paper does not give the allele frequency of HLA-B*1502 by each AED control group. Possibly this information could contain at least some data addressing if allele positive patients are less likely to be tolerant controls]

4.4 United Kingdom (M. Permohamed, senior investigator)

- Alfirevic, A., et al., *HLA-B locus in Caucasian patients with carbamazepine hypersensitivity*. Pharmacogenomics. 2006 Sep;7(6):813-8

This study found that HLA-B*1502 was not associated with carbamazepine hypersensitivity in a Caucasian population (56 patients with CBZ hypersensitivity and 43 controls). The authors did note that one patient of Asian origin with SJS/TEN who was not included in analysis due to ethnic background was positive for HLA-B*1502.

In the discussion section of the paper, the authors state that “it is interesting to note that in our study, the only patient of Asian ancestry who developed SJS with CBZ, but who has not been included in the statistical analysis due to ethnic background, was positive for the HLA-B*1502 allele.”

5. Reviewer Discussion of Published Reports

Overall Strength of Data

The association of HLA-B*1502 with CBZ-associated SJS/TEN as presented in these papers is strikingly strong. For 71 Asian subjects with SJS/TEN (60 in Taiwan, 5 in Europe, and 6 in Hong Kong) all but 1 was positive for HLA-B*1502. This is in comparison to a background rate of HLA-B*1502 of roughly 5- to 20% in these populations. While most of the cases are from Taiwan, findings are strengthened by case series in Europe and Hong Kong.

The RegiSCAR sample, while small, provides indirect evidence that Asians are affected by CBZ-associated SJS/TEN at a far higher rate than Caucasians (see also below for discussion of post-marketing evidence). Of the 12 patients with CBZ-associated SJS in the RegiSCAR report, 4 were of Asian origin. This is a far higher percentage than expected based on the percentage of Asians in these countries. The 6 countries in this group were Germany, France, Italy, Netherlands, Israel, and Austria. For all of these countries except the Netherlands, the Asian population appears to be less than 1% of the total, while for the Netherlands the Asian population is about 3%. The patients in the RegiSCAR case series were not selected by ethnicity or nationality, and effort was taken to collect all cases from the participating hospitals (it therefore seems unlikely that Asian cases were over-reported). While no data exists on the allele frequency of HLA-B*1502 specifically in Asians in these EU countries, it may be about 5-20%, as found in many Asian countries. The fact that all 4 subjects were positive for HLA-B*1502 is thus statistically unlikely, even given the small sample size.

Some theoretical possibility remain that HLA-B*1502 is not the causal allele itself, but that it is instead a marker for the presence of another closely linked allele that is usually inherited alongside it. However, HLA-B is thought to be directly involved in SJS/TEN through interaction with autoreactive T-cells, further supporting the role of this specific allele. Importantly, even if HLA-B*1502 is not itself the causative allele, its predictive value for identifying patients at risk would not be decreased (a test based on the 'true' causative allele would, however, be the most accurate).

Generalizability

The RegiSCAR findings suggest that East Asians in Europe are at increased risk of CBZ-induced SJS/TEN. There seems to be no reason why U.S. Asians would not similarly be at risk.

Essentially no information is available addressing the possible association of HLA-B*1502 with CBZ-induced SJS/TEN in non-Asian populations.

The findings of RegiSCAR and other groups indicate that HLA-B*1502 is essentially not present in Caucasian populations, or Caucasians with CBZ-associated SJS/TEN.

6. Population Genetics of HLA-B*1502

About 4- to 5% of the U.S. population, or 12 million people, self-identified as Asian in the 2000 census (Table 7). About 10% of U.S. Asians are positive for HLA-B*1502, as estimated from the

allele frequency in volunteers that self-identified as Asian/Pacific Islander in the National Marrow Donor Program. More detailed information on the origin of these subjects, or on the allele frequency in specific U.S. Asian subgroups is not available (personal communication,). Within Asian subgroups (based on country of origin, but presumably true in the U.S.), the allele frequency for HLA-B*1502 varies widely, from 0.2% for Japanese, to 36% in a Filipino ethnic subgroup (Table 8).

A small percentage, perhaps 0.4% or less of African Americans also are positive for this allele. HLA-B*1502 is essentially absent from African populations other than those with some Asian ancestry.

The frequency of the allele in U.S. *South* Asian Indians is not known. The allele frequency in India is 2% in a population identified as “North Hindus.” This might reflect the allele frequency in much of the U.S. South Asian population. However, the allele frequency is higher, up to 12%, in some South Asian subpopulations.

The allele is essentially absent from U.S. Caucasians, Hispanics, and Native Americans.

Table 7: U.S. Asian Population Subgroups

Asian Population by Detailed Group: 2000

(For information on confidentiality protection, nonsampling error, and definitions, see www.census.gov/prod/cen2000/doc/sf1.pdf)

Detailed group	Asian alone		Asian in combination with one or more other races		Asian detailed group alone or in any combination ²
	One Asian group reported ¹	Two or more Asian groups reported ²	One Asian group reported	Two or more Asian groups reported ²	
Total	10,019,405	223,593	1,516,841	138,989	11,898,828
Asian Indian	1,678,765	40,013	165,437	15,384	1,899,599
Bangladeshi	41,280	5,625	9,655	852	57,412
Bhutanese	183	9	17	3	212
Burmese	13,159	1,461	1,837	263	16,720
Cambodian	171,937	11,832	20,830	1,453	206,052
Chinese, except Taiwanese	2,314,537	130,826	201,688	87,790	2,734,841
Filipino	1,850,314	57,811	385,236	71,454	2,364,815
Hmong	169,428	5,284	11,153	445	186,310
Indo Chinese	113	55	23	8	199
Indonesian	39,757	4,429	17,256	1,631	63,073
Iwo Jiman	15	3	60	-	78
Japanese	796,700	55,537	241,209	55,486	1,148,932
Korean	1,076,872	22,550	114,211	14,794	1,228,427
Laotian	168,707	10,396	17,914	1,186	198,203
Malaysian	10,690	4,339	2,837	700	18,566
Maldivian	27	2	22	-	51
Nepalese	7,858	351	1,128	62	9,399
Okinawan	3,513	2,625	2,816	1,645	10,599
Pakistani	153,533	11,095	37,587	2,094	204,309
Singaporean	1,437	580	307	70	2,394
Sri Lankan	20,145	1,219	2,966	257	24,587
Taiwanese	118,048	14,096	11,394	1,257	144,795
Thai	112,989	7,929	27,170	2,195	150,283
Vietnamese	1,122,528	47,144	48,639	5,425	1,223,736
Other Asian, not specified ³	146,870	19,576	195,449	7,535	369,430

- Represents zero.

¹The total of 10,019,405 respondents categorized as reporting only one Asian group in this table is lower than the total of 10,019,410 shown in Table PCT5 (U.S. Census Bureau, Census 2000 Summary File 1 100-Percent Data, see factfinder.census.gov). This table includes more detailed groups than PCT5. This means that, for example, an individual who reported "Pakistani and Nepalese" is shown in this table as reporting two or more Asian groups. However, that same individual is categorized as reporting a single Asian group in PCT5 because both Pakistani and Nepalese are part of the larger Other specified Asian group.

²The numbers by detailed Asian group do not add to the total population. This is because the detailed Asian groups are tallies of the number of Asian responses rather than the number of Asian respondents. Respondents reporting several Asian groups are counted several times. For example, a respondent reporting "Korean and Filipino" would be included in the Korean as well as the Filipino numbers.

³Includes respondents who checked the "Other Asian" response category on the census questionnaire or wrote in a generic term such as "Asian" or "Asiatic."

Source: U.S. Census Bureau, Census 2000, special tabulations.

Table 8: Populations Positive for HLA-B*1502

Population	Phenotype Frequency(%)
<u>China North Han</u>	4
<u>China South Han</u>	14
<u>Hong Kong Chinese</u>	20
<u>India Khandesh Pawra (Tribal minority)</u>	12
<u>India Mumbai Marathas (Large minority)</u>	4

India North Hindus (Majority)	2
Italy South Campania	0.2
Japan Central	0.2
Philippines, Ivatan (Minority)	36
Indonesians (sample from Singapore)	16
Malay (sample from Singapore)	16
South Korea	0.4
Spain Eastern Andalusia Gypsy	2
Taiwan Hakka (10% of pop.)	5.5
Taiwan Minnan (80% of pop.)	10.8
Thailand	16

7. Spontaneous Adverse Events Reports

This section of the review analyzes international spontaneous adverse events reports of CBZ-associated SJS/TEN. Datasets were received from both the World Health Organization (WHO) and Novartis (sponsor for Tegretol).

Spontaneous adverse events reported to FDA do not generally contain information about race/ethnicity.

7.1 WHO Spontaneous Adverse Events Data

Data from the WHO Uppsala Monitoring Center (Who-UMC) is shown in Table 9. Notably, reports of CBZ-associated SJS and TEN from the two Asian countries, Malaysia and Thailand, are far higher than reports from the predominantly Caucasian countries.

Table 9: WHO-UMC CBZ SJS/TEN Reports, 1995-2006

Country	SJS + TEN reports/	SJS reports total	TEN reports total	All AE reports (per million people)
Malaysia				

Thailand	
Sweden	
Switzerland	
Germany	
United Kingdom	
Canada	
Netherlands	
Spain	
United States	
Denmark	
Italy	

[Comment: In a separate study, CBZ was reported to be the commonest cause of EM, SJS and TEN in Malaysia (Kamaliah et al., 1998, *Erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis in North Eastern Malaysia*. Int J Dermatol;37:520-3).]

7.2 Novartis Postmarketing Experience

Novartis, the sponsor for Tegretol, provided postmarketing data that similarly shows an apparent increased rate of reporting of CBZ-associated SJS/TEN in some Asian countries (Table 10). The reported incidence of SJS is about 10-fold higher in Taiwan, Philippines, and Malaysia versus other, predominantly Caucasian countries. The incidence in Japan is less strikingly increased.

Table 10: Novartis CBZ SJS/TEN Reports, 2000-2006

Table 5-3 Cumulative estimated reported rates between 2000 and 2006 expressed as events for 100000 Patient Year Exposure

Countries	Patient Year Exposure	All events	Severe Reactions	Skin SJS	TEN
Total	11617732	125	14	4	1
USA	1164121	140	4	2	0
Australia	248563	735	18	6	2
Brazil	456877	831	10	3	0
France	731678	952	43	4	1
United Kingdom	758986	642	20	6	3
India	1005581	39	6	1	1
Italy	763074	82	8	2	0
Japan	753093	1536	112	13	4
Malaysia	56501	271	69	37	4
Philippines	43430	336	76	53	2
Taiwan	109329	262	102	54	5
South Africa	234634	126	5	3	0

Of note, the annual reporting rates in each country over this time period were far from stable (data not shown). For example, the reporting rate in the Novartis data for the U.S. declined dramatically (by about a factor of 10), far higher than the roughly decline in CBZ prescriptions. In the same period, FDA fairly consistently received about 10 reports/year of CBZ-associated SJS/TEN. The number of reports in the Novartis data is also lower than the WHO data for countries in common in the two lists, United States, United Kingdom, Italy, and Malaysia. Also, there was no reporting from Malaysia, Philippines, and Taiwan in the first 2 years of this time interval.

8. Sponsor Analysis of CBZ-SJS/TEN Association

Sponsors for CBZ were asked by FDA to address the following issues:

- Submit a report which comprehensively addresses these data (Hung, et al 2006 and Lonjou, et al 2006), and any other pertinent information concerning cutaneous adverse drug reactions related to CBZ.
- The possibility that an unacceptably high risk of severe cutaneous events may be predictable and avoidable for some patients who might be candidates for carbamazepine.
- The need for labeling changes based on your review of this new information.

Following is a review of the submission from Novartis, sponsor of Tegretol, and from Shire, sponsor for Carbatrol and Equetro.

8.1 Novartis (Tegretol)

8.1.1 Overall Novartis Conclusions

Novartis concludes that a correlation between the incidence of SJS/TEN and the presence of the HLA-B*1502 allele is reasonably established in a predominantly Taiwanese Han Chinese population. Based on this, Novartis states the following:

“In addressing the need for possible changes to the Tegretol prescribing information, Novartis believes that the genetic susceptibility for CBZ associated SJS/TEN has not been completely worked out and that further investigation needs to be performed. However, available post-marketing adverse event data demonstrate a pattern of higher estimated reporting rates for CBZ associated SJS in some Asian countries (e.g., Taiwan, Malaysia, the Philippines and Japan). Recognizing the diverse plurality of the United States population, Novartis seeks the opportunity to discuss with FDA whether changes to the Tegretol prescribing information are needed to provide guidance to physicians when considering to prescribe the drug to patients of Asian origin and, if so, determine what language would be appropriate for this purpose.”

Novartis expresses the following concerns regarding potential changes to CBZ labeling [reviewer note: most relevant of sponsor concerns selected]:

- HLA-B*1502 testing is not available at “point of care,” which may be an impediment to appropriate clinical decision making.
- Available tests for HLA-B*1502 have unknown sensitivity, specificity, and reproducibility.
- The recommendations to patients testing positive would need to consider that alternative therapies cannot be assumed SJS/TEN risk free. [Comment: particularly for drugs such as phenytoin, Phenobarbital, and lamotrigine]
- The generalizability of the findings to other populations is unknown.
- Without specific testing for the presence of the HLA-B*1502 allele the predictive value of selective withholding of Tegretol from Asian patients cannot be determined.
- Without a clear assessment of the risk of genetic susceptibility of CBZ associated SJS-TEN the ability to avoid SJS or TEN in ethnic populations in the USA cannot be reliably estimated. [Note: the above two concerns appear to reflect the lack of information in the U.S., and the difficulty of collecting information given the rarity of the event].

8.1.2 Novartis Analysis

Novartis estimated characteristics of a test of HLA-B*1502 to prevent SJS/TEN (Table 11). They used both the higher estimate of incidence of SJS/TEN in Taiwan, as reported by Hung 2006, and a lower estimate from China (Li and Ma, 2006, *Clinical and Experimental Dermatology*, 31, 642-647).

[Comment: Importantly, Li and Ma calculated risk of SJS/TEN per million *total population*, not per million new CBZ *users*. The ‘Alternative’ estimate provided by the sponsor is therefore not comparable to the estimate by Hung. Li and Ma did find that CBZ was responsible for more cases of SJS/TEN in their regional hospital than any other drug or drug class].

Table 11: HLA-B*1502 Test Characteristics, Novartis Estimate

Table 4-1 Plausible testing scenarios based on data presented by Hung et al (2006), Li et al (2006) and Tennis et al (1997), with their corresponding potential test information*

Scenario	Percentage of SJS/TEN cases with B*1502 allele	Risk of SJS/TEN per million new users	Percentage of controls with B*1502 allele	Number of patients needed to test to prevent one SJS/TEN	Number of false positives for each prevented SJS/TEN	Positive predictive value (ppv) (%)
Hung 2006	98.3	2500	4.2	408	17	5.58
Alternative [‡]	98.3	610	4.2	1660	69	1.42

* Negative predictive value for both scenarios in the table is greater than 99.9%

[‡] The risk of SJS per million new users reported by Tennis et al is used in the alternative plausible scenario because Li LF and Ma C report an incidence density per million person-years similar to the one reported for Caucasians.

[Comment: The Novartis calculation is in general agreement with that of Hung 2005, and my calculations in this review.]

8.2 Shire (Carbatrol, Equetro)

Shire believes that labeling changes for Carbatrol and Equetro are not appropriate at this time.

Carbatrol and Equetro are marketed only in the United States. Shire received 10 spontaneously reported cases of SJS (7), SJS/TEN (2), or TEN (1) associated with Carbatrol from 1997 to 2007. No ethnicity information was provided to Shire in these reports. These reports yield an estimated reporting rate for SJS/TEN of 2 events per 100,000 patient-years exposure. One report of SJS was received for Equetro between 2004 and 2007. The patient was Caucasian. This single report yields an estimated reporting rate for SJS/TEN was 8 events per 100,000 patient-years of exposure to Equetro.

9. HLA-B*1502 Genetic Testing

HLA testing is readily available through commercial clinical laboratories and major medical centers. For example, Labcorp (Herndon, VA) performs high-resolution HLA-B genotyping, including HLA-B*1502. Test results are available in 3- to 5 days, for a cost of about \$200. No HLA test is available as a “point of care” test. Some HLA tests are FDA-cleared through the 510(K) process. To obtain 510(K) clearance, the sponsor is required only to demonstrate substantial equivalence to a currently cleared HLA test of their own choosing. There is no

requirement to otherwise determine sensitivity or specificity of the test versus a ‘gold standard’ such as bidirectional DNA sequencing. HLA tests are also available that were developed in certified laboratories, but that are not FDA-cleared. No HLA-B genotyping test has been FDA *licensed* for diagnosis of a specific disease, or for a specific clinical indication. Instead, test results are interpreted and used by the individual physician as the clinical situation warrants.

HLA-B tests might most accurately be understood as a combination of tests designed to identify multiple DNA sequence variations in the HLA-B gene among individuals. New HLA-B genotypes are continually being identified (currently more than 300 are known worldwide), and test components are regularly added to FDA cleared tests without regulatory oversight or action. Technically, adding a new genotype to a test most often involves designing specific PCR primers for that new genotype, and specifying PCR-amplification conditions. Some differences in the performance of different PCR primers is to be expected, such that differences exist in the sensitivity and specificity for detecting each specific allele, even in the context of a single ‘cleared HLA-B test.’

HLA testing can also involve a series of sequential steps of increasing resolution, designed to achieve the desired degree of test accuracy. This makes it difficult to define test performance using the usual parameters. For example, B*1502 can be excluded in the majority of patients by low to intermediate resolution typing methods. For example, if the patient carries B*39/B*39 as determined by intermediate resolution testing, then all B*15 alleles are excluded, including B*1502. If a B*15 allele is detected using lower resolution methods, B*1502 can not be excluded without higher resolution testing.

Voluntary accreditation of laboratories providing histocompatibility testing is provided by The American Society of Histocompatibility and Immunogenetics, a not-for-profit association. While laboratories are required to correctly identify test samples to maintain accreditation, this can not readily be used to estimate the test characteristics for a specific allele.

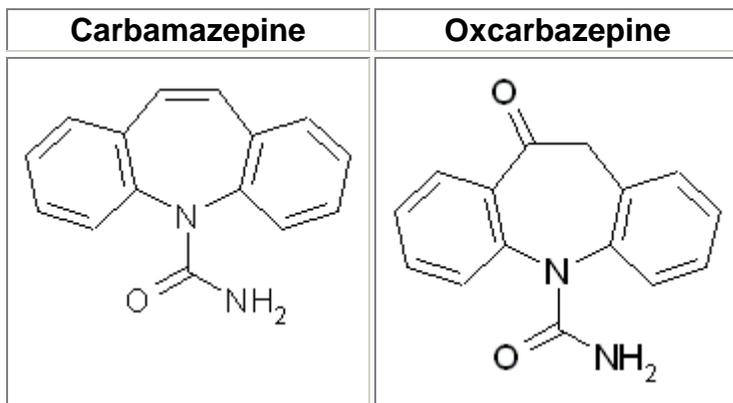
9.1 Potential Cross-Sensitivity to SJS/TEN from other AEDs

Cross-sensitivity particularly to non-serious rash induced by AEDs is thought to occur in some patients (Hyson and Sadler, 1997, *Can J. Neurol. Sci.*, 24(3):245-9). This raises concern that cross-sensitivity might also exist for AED-induced SJS/TEN. However, essentially no data is available to address this concern. Two HLA-B*1502 positive patients in the Hong Kong cohort had SJS/TEN related to phenytoin and lamotrigine, but 15% of the control group was also positive, such that little can be concluded about susceptibility of HLA-B*1502 positive patients to SJS/TEN from these AEDs.

10. Oxcarbazepine (Trileptal)

Oxcarbazepine and CBZ are very closely related structurally (Figure 1). No data is available addressing the association of HLA-B*1502 and oxcarbazepine-associated SJS/TEN. Cross-reactivity to serious skin reactions had been reported for CBZ and oxcarbazepine (Beran, 1993, *Epilepsia* 34(1):163-5).

Figure 1: CBZ and Oxcarbazepine Structure



The Trileptal label contains the following recommendation regarding cross-reactivity with CBZ:

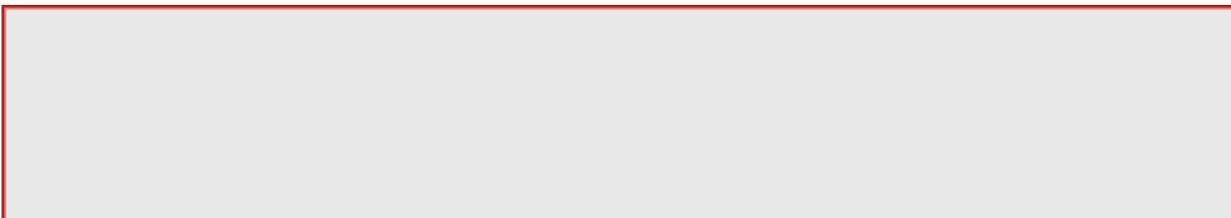
From **WARNINGS**

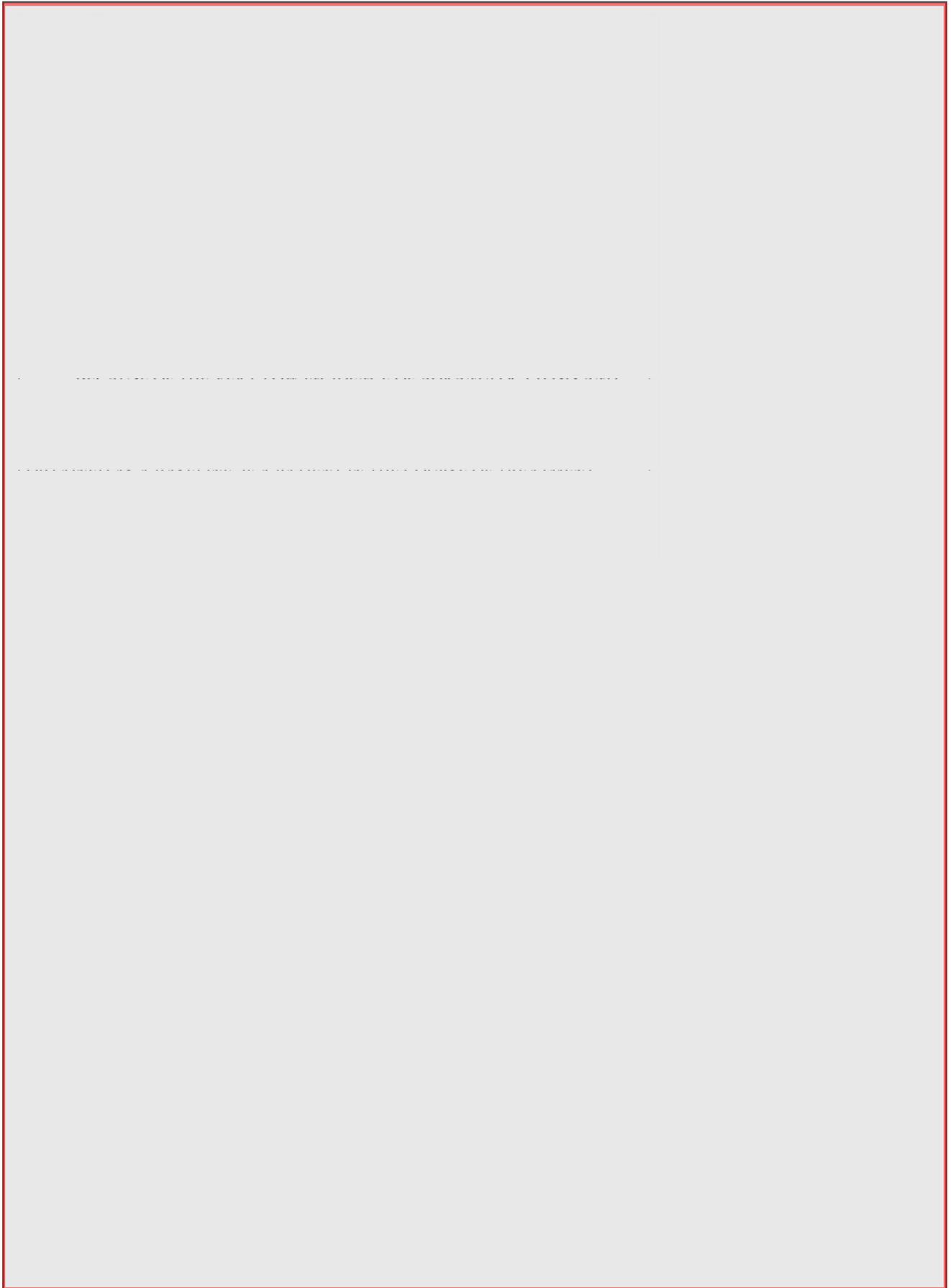
“Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25%-30% of them will experience hypersensitivity reactions with Trileptal. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Trileptal only if the potential benefit justifies the potential risk.”

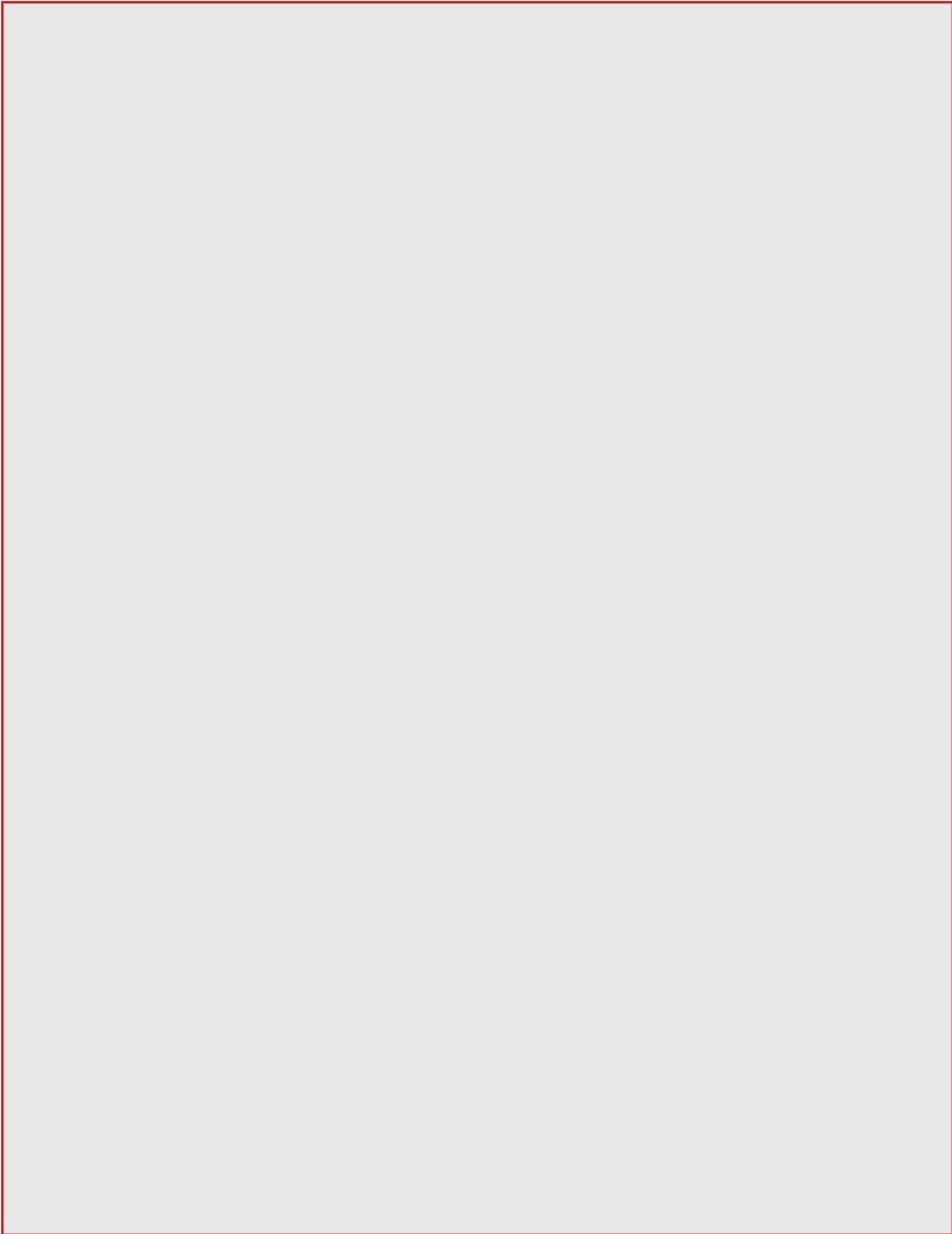
The oxcarbazepine label additionally states that patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Trileptal only if the potential benefit justifies the potential risk.

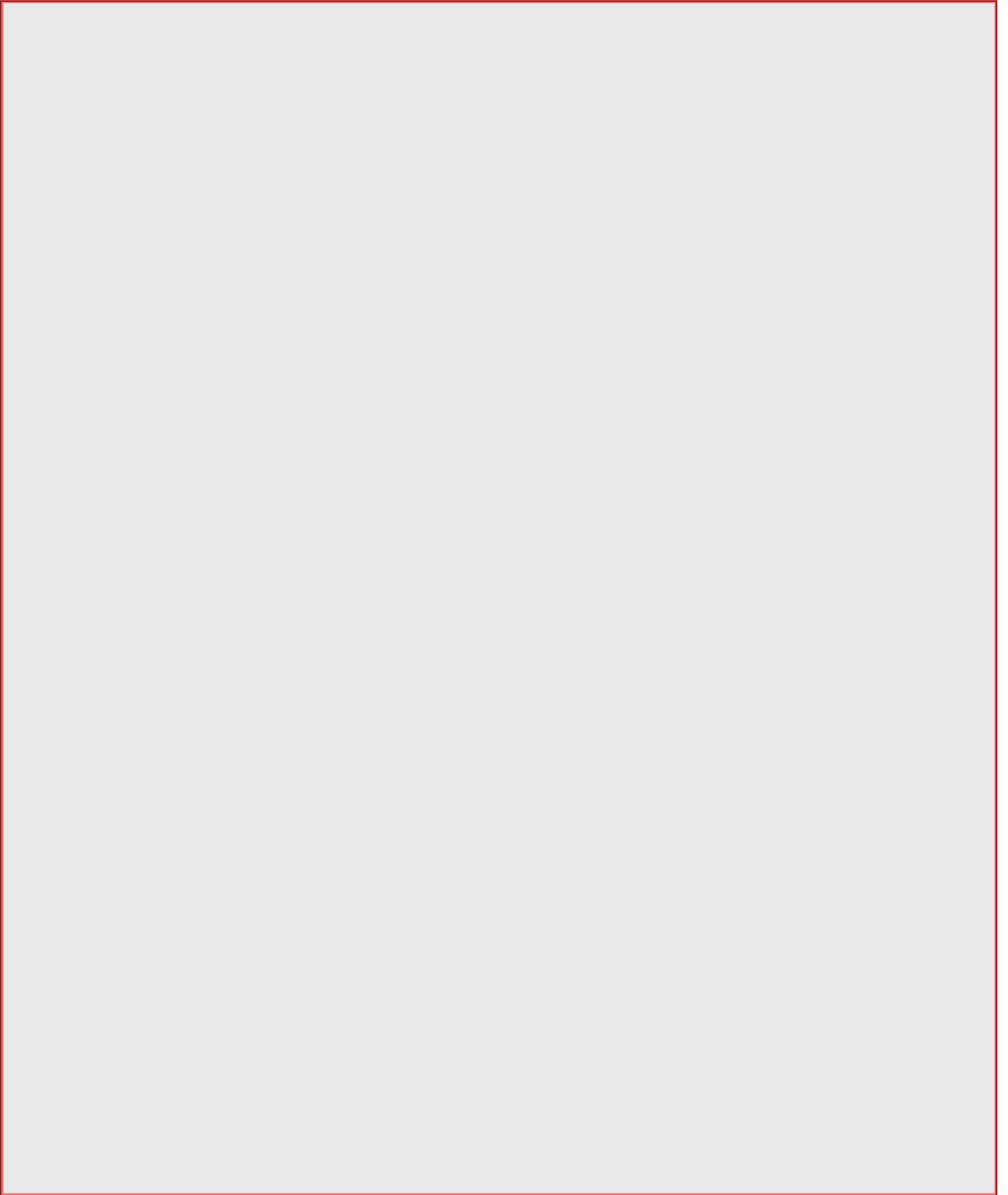
[Comment: In the absence of data, it would seem prudent for patients positive for HLA-B*1502 to avoid AEDs that are structurally related to CBZ (phenytoin, Phenobarbital, oxcarbazepine), or that are associated with a high rate of SJS/TEN (lamotrigine). The potential for increased sensitivity to these other AEDs could be addressed experimentally, and labeling liberalized if findings are reassuring.]

11. Draft Proposed Changes to CBZ Labeling











13. Future Studies

The following are important areas of incomplete understanding of CBZ associated SJS/TEN. Studies to address these areas would benefit safe use of CBZ:

- Risk of SJS/TEN in HLA-B*1502 positive U.S. patients exposed to CBZ
With current data the possibility can not be completely ruled out that the risk of CBZ-associated SJS/TEN for U.S. patients of Asian descent is different than the risk to patients in other countries. Since the risk appears increased in several

different geographic areas (Taiwan, Hong Kong, Europe), this possibility seems unlikely. However, to understand the effectiveness of any program to reduce risk that is adopted in the U.S., some knowledge of past risk would clearly be beneficial. Given the apparent strength of the genetic association of HLA-B*1502 and SJS/TEN, data from only a few U.S. patients (perhaps only 5- to 10) could contribute important risk information if allele-positive patients were over-represented.

- Risk of SJS/TEN in HLA-B*1502 positive *non-East Asian* patients
Currently, almost no data exists addressing possible increased risk of CBZ-associated SJS/TEN in non-East Asian carriers of HLA-B*1502. In particular, about 2% of *South* Asians (higher in some South Asian minorities) carries HLA-B*1502, while several populations carry the allele at a frequency closer to 0.5%. Case series from India document that CBZ is commonly associated with SJS/TEN in comparison to other drugs (up to 44% of Indian patients in Devi et al., 2005, *Indian J. Dermatol Venereol Leprol.*, 71(5):325-8). However, this suggestive data lacks information about relative CBZ usage (which might be high in India), and HLA genotype.
- Other Anti-epileptics
The risk of SJS/TEN is unknown in patients positive for HLA-B*1502 who are exposed to AEDs other than CBZ. Phenytoin, phenobarbital, oxcarbazepine and lamotrigine are of particular concern because they are individually associated with SJS/TEN and/or structurally related to carbamazepine. Genotype data from only a few patients who developed SJS/TEN from these other AEDs could contribute important risk information if HLA-B*1502 positive patients are over-represented.
- Test performance of genotyping for HLA-B*1502.
No information is currently available about the performance of tests for HLA-B*1502 in preventing CBZ-associated SJS/TEN. Prospectively evaluating test performance is problematic, because exposing HLA-B*1502 patients to CBZ would not be acceptable.

14. Appendix: Current Tegretol Label



Tegretol[®]
carbamazepine USP

Chewable Tablets of 100 mg - red-speckled, pink Tablets of 200 mg – pink
Suspension of 100 mg/5 mL

Tegretol[®]-XR (carbamazepine extended-release tablets) 100 mg, 200 mg, 400
mg

Rx only

Prescribing Information

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable

Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive

Ingredients

Tablets: Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only),

DESCRIPTION

tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon). Its chemical name is 5*H*-dibenz[*b,f*]azepine-5-carboxamide, and its structural formula is



flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Suspension: Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrans, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, titanium dioxide (200-mg tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

Mechanism of Action

Tegretol has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of Tegretol, carbamazepine-10,11-epoxide, has anticonvulsant activity as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of Tegretol has not been established.

Pharmacokinetics

In clinical studies, Tegretol suspension, conventional tablets, and XR tablets delivered equivalent amounts of drug to the systemic circulation. However, the suspension was absorbed somewhat faster, and the XR tablet slightly slower, than the conventional tablet. The bioavailability of the XR tablet was 89% compared to suspension. Following a b.i.d. dosage regimen, the suspension provides higher peak levels and lower trough levels than those obtained from the conventional tablet for the same dosage regimen. On the other hand, following a t.i.d. dosage regimen, Tegretol suspension affords steady-state plasma levels comparable to Tegretol tablets given b.i.d. when administered at the same total mg daily dose. Following a b.i.d. dosage regimen, Tegretol-XR tablets afford steady-state plasma levels comparable to conventional Tegretol tablets given q.i.d., when administered at the same total mg daily dose. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/mL, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/mL. In polytherapy, the concentration of Tegretol and concomitant drugs may be increased or decreased during therapy, and drug effects may be altered (see PRECAUTIONS, Drug Interactions). Following chronic oral administration of suspension, plasma levels peak at approximately 1.5 hours compared to 4-5 hours after administration of conventional Tegretol tablets, and 3-12 hours after administration of Tegretol-XR tablets. The CSF/serum ratio is 0.22, similar to the 24% unbound Tegretol in serum. Because Tegretol induces its own metabolism, the half-life is also variable. Autoinduction is completed after 3-5 weeks of a fixed dosing regimen. Initial half-life values range from 25-65 hours, decreasing to 12-17 hours on repeated doses. Tegretol is metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide from Tegretol. After oral administration of ¹⁴C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol.

The pharmacokinetic parameters of Tegretol disposition are similar in children and in adults. However, there is a poor correlation between plasma concentrations of carbamazepine and Tegretol dose in children. Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide (a metabolite shown to be equipotent to carbamazepine as an anticonvulsant in animal screens) in the

younger age groups than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age (in one report from 0.44 in children below the age of 1 year to 0.18 in children between 10-15 years of age).

The effects of race and gender on carbamazepine pharmacokinetics have not been systematically evaluated.

INDICATIONS AND USAGE

Epilepsy

Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

- 1 Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
 - 2 Generalized tonic-clonic seizures (grand mal).
 - 3 Mixed seizure patterns which include the above, or other partial or generalized seizures.
- Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia

Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hepatic porphyrias (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda), hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported. If a patient develops a skin reaction while taking Tegretol, consideration should be given to discontinuing Tegretol use.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

As with all antiepileptic drugs, Tegretol should be withdrawn gradually to minimize the potential of increased seizure frequency.

Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. There have been reports in association with carbamazepine of other congenital anomalies and developmental disorders (e.g., craniofacial defects, cardiovascular malformations, hypospadias, and anomalies involving various body systems). In treating or counseling women of childbearing potential, the prescribing physician will wish to weigh the benefits of therapy against the risks. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, if therapy is to be continued, monotherapy may be preferable for pregnant women.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect defects using currently accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal Tegretol use. These symptoms may represent a neonatal withdrawal syndrome.

PRECAUTIONS

General

Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac conduction disturbance; cardiac, hepatic, or renal damage; adverse hematologic or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with Tegretol.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (see ADVERSE REACTIONS and PRECAUTIONS, Laboratory Tests). In some cases, hepatic effects may progress despite discontinuation of the drug.

Multi-organ hypersensitivity reactions which can affect the skin, liver, hematopoietic organs and lymphatic system or other organs and occurring days to weeks or months after initiating treatment have been reported in rare cases (see ADVERSE REACTIONS, Other and PRECAUTIONS, Information for Patients).

Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

In patients who have exhibited hypersensitivity reactions to carbamazepine approximately 25 to 30 % of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal®).

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects (see DOSAGE AND ADMINISTRATION).

Tegretol suspension contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Patients should be advised that serious skin reactions have been reported in association with Tegretol. In the event a skin reaction should occur while taking Tegretol, patients should consult

with their physician immediately (see Warnings).

Caution should be exercised if alcohol is taken in combination with Tegretol therapy, due to a possible additive sedative effect.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur (see PRECAUTIONS, General and ADVERSE REACTIONS). Carbamazepine should be discontinued, based on clinical judgment, if indicated by newly occurring or worsening clinical or laboratory evidence of liver dysfunction or hepatic damage, or in the case of active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Interference with some pregnancy tests has been reported.

Drug Interactions

There has been a report of a patient who passed an orange rubbery precipitate in his stool the day after ingesting Tegretol suspension immediately followed by Thorazine[®] solution. Subsequent testing has shown that mixing Tegretol suspension and chlorpromazine solution (both generic and brand name) as well as Tegretol suspension and liquid Mellaril[®] resulted in the occurrence of this precipitate. Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medicinal agents or diluents. (see DOSAGE AND ADMINISTRATION).

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to, the following:

Agents That May Affect Tegretol Plasma Levels

CYP 3A4 inhibitors inhibit Tegretol metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include

cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, nefazodone, trazodone, loxapine*, olanzapine, quetiapine*, loratadine, terfenadine, omeprazole, oxybutynin, dantrolene, isoniazid, niacinamide, nicotinamide, ibuprofen, propoxyphene, azoles (e.g., ketoconazole, itraconazole, fluconazole, voriconazole), acetazolamide, verapamil, ticlopidine, grapefruit juice, protease inhibitors, valproate.*

CYP 3A4 inducers can increase the rate of Tegretol metabolism. Drugs that have been shown, or that would be expected, to decrease plasma carbamazepine levels include

cisplatin, doxorubicin HCl, felbamate,[†] fosphenytoin, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline, aminophylline.

*increased levels of the active 10,11-epoxide

[†]decreased levels of carbamazepine and increased levels of the 10,11-epoxide

Effect of Tegretol on Plasma Levels of Concomitant Agents

Increased levels: clomipramine HCl, phenytoin, primidone

Tegretol is a potent inducer of hepatic CYP3A4 and may therefore reduce plasma concentrations of comedications mainly metabolized by 3A4 through induction of their metabolism. Tegretol causes, or would be expected to cause, decreased levels of the following:

acetaminophen, alprazolam, bupropion, dihydropyridine calcium channel blockers (e.g., felodipine), citalopram, cyclosporine, corticosteroids (e.g., prednisolone, dexamethasone), clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, midazolam, oral and other hormonal contraceptives, oxcarbazepine, phenoximide, phenytoin, praziquantel, protease inhibitors, risperidone, theophylline, tiagabine, topiramate, tramadol, trazodone, tricyclic antidepressants (e.g., imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Concomitant medication with Tegretol and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.

Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g., pancuronium.) Their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Concomitant use of Tegretol with hormonal contraceptive products (e.g., oral, and levonorgestrel subdermal implant contraceptives) may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended

pregnancies have been reported. Alternative or back-up methods of contraception should be considered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy

Pregnancy Category D (see WARNINGS).

Labor and Delivery

The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers

Tegretol and its epoxide metabolite are transferred to breast milk. The ratio of the concentration in breast milk to that in maternal plasma is about 0.4 for Tegretol and about 0.5 for the epoxide. The estimated doses given to the newborn during breast feeding are in the range of 2-5 mg daily for Tegretol and 1-2 mg daily for the epoxide.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Substantial evidence of Tegretol's effectiveness for use in the management of children with epilepsy (see Indications for specific seizure types) is derived from clinical investigations performed in adults and from studies in several in vitro systems which support the conclusion that (1) the pathogenetic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children.

Taken as a whole, this information supports a conclusion that the generally accepted therapeutic range of total carbamazepine in plasma (i.e., 4-12 mcg/mL) is the same in children and adults.

The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer-term data from clinical trials is available.

Geriatric Use

No systematic studies in geriatric patients have been conducted.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin, liver, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, anemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism (e.g., pulmonary embolism), and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure.

Pancreatic: Pancreatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported. There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

Testicular atrophy occurred in rats receiving Tegretol orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, hyperacusis, neuroleptic malignant syndrome.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported both with and without concomitant use of psychotropic drugs.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered punctate cortical lens opacities, increased intraocular pressure as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests). Decreased levels of plasma calcium leading to osteoporosis have been reported.

Other: Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases. Signs or symptoms may include, but are not limited to fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests. These signs and symptoms may occur in various combinations and not necessarily concurrently. Signs and symptoms may initially be mild. Various organs, including but not limited to, liver, skin, immune system, lungs, kidneys, pancreas, myocardium, and colon may be affected (see PRECAUTIONS, General and PRECAUTIONS, Information for Patients).

Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, 3.2 g (a 24-year-old woman died of a cardiac arrest and a 24-year-old man died of pneumonia and hypoxic encephalopathy); children, 4 g (a 14-year-old girl died of a cardiac arrest), 1.6 g (a 3-year-old girl died of aspiration pneumonia).

Oral LD₅₀ in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea

pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (> 60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in

children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdose or in recent therapy (within 1 week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet, and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) Fe-ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A₂ and F hemoglobin, and (7) serum folic acid and B₁₂ levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION (SEE TABLE BELOW)

Tegretol suspension in combination with liquid chlorpromazine or thioridazine results in precipitate formation, and, in the case of chlorpromazine, there has been a report of a patient passing an orange rubbery precipitate in the stool following coadministration of the two drugs. (See PRECAUTIONS, Drug Interactions.) Because the extent to which this occurs with other liquid medications is not known, Tegretol suspension should not be administered simultaneously with other liquid medications or diluents.

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Medication should be taken with meals.

Since a given dose of Tegretol suspension will produce higher peak levels than the same dose given as the tablet, it is recommended to start with low doses (children 6-12 years: 1/2 teaspoon q.i.d.) and to increase slowly to avoid unwanted side effects.

Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).

Tegretol-XR is an extended-release formulation for twice-a-day administration. When converting patients from Tegretol conventional tablets to Tegretol-XR, the same total daily mg dose of Tegretol-XR should be administered. **Tegretol-XR tablets must be swallowed whole and never crushed or chewed.** Tegretol-XR tablets should be inspected for chips or cracks. Damaged tablets, or tablets without a release portal, should not be consumed. Tegretol-XR tablet coating is not absorbed and is excreted in the feces; these coatings may be noticeable in the stool.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age - Initial: Either 200 mg b.i.d. for tablets and XR tablets, or 1 teaspoon q.i.d. for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily in children 12-15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. **Maintenance:** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age - Initial: Either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. **Maintenance:** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Children under 6 years of age - Initial: 10-20 mg/kg/day b.i.d. or t.i.d. as tablets, or q.i.d. as suspension. Increase weekly to achieve optimal clinical response administered t.i.d. or q.i.d. **Maintenance:** Ordinarily, optimal clinical response is achieved at daily doses below 35 mg/kg. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses above 35 mg/kg/24 hours can be made.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions, and Pregnancy Category D).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: On the first day, either 100 mg b.i.d. for tablets or XR tablets, or 1/2 teaspoon q.i.d. for suspension, for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg/day using increments of 100 mg every 12 hours for tablets or XR tablets, or 50 mg (1/2 teaspoon) q.i.d. for suspension, only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400-800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

Dosage Information

Indication	Initial Dose			Subsequent Dose		
	Tablet*	XR†	Suspension	Tablet*	XR† Suspension	Maximum Daily Administration
Epilepsy Under 6 yr	10-20 mg/kg/day b.i.d. or t.i.d.		10-20 mg/kg/day q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	Increase weekly to achieve optimal clinical response, t.i.d. or q.i.d.	35 mg/kg/24 hr (see section above) Administration

6-12 yr	100 mg b.i.d. (200 mg/day)	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 100 mg/day at weekly intervals, t.i.d. or q.i.d.	Add 100 mg/day at weekly intervals, b.i.d. Add up to 1 tsp (100 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr
Over 12 yr	200 mg b.i.d. (400 mg/day)	200 mg b.i.d. (400 mg/day)	1 tsp q.i.d. (400 mg/day)	Add up to 200 mg/day at weekly intervals, t.i.d. or q.i.d.	Add up to 200 mg/day at weekly intervals, b.i.d. Add up to 2 tsp (200 mg)/day at weekly intervals, t.i.d. or q.i.d.	1000 mg/24 hr 1600 mg/24 hr
Trigeminal Neuralgia	100 mg b.i.d. (200 mg/day)	100 mg b.i.d. (200 mg/day)	½ tsp q.i.d. (200 mg/day)	Add up to 200 mg/day in increments of 100 mg every 12 hr	Add up to 200 mg/day in increments of 100 mg every 12 hr Add up to 2 tsp (200 mg)/day in increments of 50 mg (½ tsp) q.i.d.	1200 mg/24 hr

*Tablet = Chewable or conventional tablets
 †XR = Tegretol[®]-XR extended-release tablets

HOW SUPPLIED

Chewable Tablets 100 mg - round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

- Bottles of 100.....NDC 0083-0052-30
- Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0083-0052-32

Do not store above 30 °C (86 °F). *Protect from light and moisture.*
Dispense in tight, light-resistant container (USP).
Meets USP Dissolution Test 1.

Tablets 200 mg - capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the partially scored side)

- Bottles of 100.....NDC 0083-0027-30
- Bottles of 1000.....NDC 0083-0027-40
- Unit Dose (blister pack)
- Box of 100 (strips of 10).....NDC 0083-0027-32 Do not

store above 30 °C (86 °F). *Protect from moisture. Dispense in tight container (USP).* *Meets USP Dissolution Test 2.*

XR Tablets 100 mg - round, yellow, coated (imprinted T on one side and 100 mg on the other), release portal on one side

- Bottles of 100.....NDC 0083-0061-30 **XR**

Tablets 200 mg - round, pink, coated (imprinted T on one side and 200 mg on the other), release portal on one side

- Bottles of 100.....NDC 0083-0062-30 **XR**

Tablets 400 mg - round, brown, coated (imprinted T on one side and 400 mg on the other), release

portal on one side

Bottles of 100.....NDC 0083-0060-30 Store at controlled room temperature 15 °C-30 °C (59 °F-86 °F). *Protect from moisture. Dispense in tight container (USP).*

Suspension 100 mg/5 mL (teaspoon) -yellow-orange, citrus-vanilla flavored

Bottles of 450 mL.....NDC 0083-0019-76 Shake well before using. Do not store above 30 °C (86 °F). *Dispense in tight, light- resistant container (USP).* *Thorazine® is a registered trademark of GlaxoSmith Kline. Tegretol Chewable Tablets Manufactured by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

Tegretol Suspension Manufactured by: Patheon Inc. Whitby Operations Whitby Ontario, Canada L1N 5Z5



Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

REV: SEPTEMBER 2006

© Novartis Tegretol Tablets Manufactured by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

Tegretol-XR Tablets Manufactured by: Novartis Pharma GmbH D-79664 Wehr, Germany

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ronald Farkas
10/11/2007 05:28:47 PM
MEDICAL OFFICER

John Feeney
10/26/2007 10:34:59 PM
MEDICAL OFFICER
Concur