HLA: lamotrigine 6932

95% CI = 95% confidence interval, DRESS = drug reaction with eosinophilia and systemic symptoms, also known as hypersensitivity syndrome (HSS), HLA = human leukocyte antigen, HSS = hypersensitivity syndrome, including DRESS, NS = not significant, OR = odds ratio, S = significant, SJS = Stevens-Johnson syndrome, SmPC = summary of product characteristics, TEN = toxic epidermal necrolysis

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, then the health care professional should consider the next best option.

Brief summary and justification of choices:
Lamotrigine can induce the life-threatening cutaneous adverse events SJS/TEN and DRESS. According to the SmPC Lamictal (lamotrigine) 26-01-22, the incidence of SJS/TEN is 0.1% and the incidence of DRESS < 0.01% of adult users and the incidence of skin rash necessitating hospital admission is 0.3-1% in paediatric users. Lamotrigine can also induce mild maculopapular exanthema, but this was not investigated in the risk analysis. The hypersensitivity reactions generally develop between 2 weeks and 3 months after the start of lamotrigine.
Because specific HLA proteins are involved in specific cellular immune reactions that cause specific hypersensitivity reactions, HLA proteins can affect the risk of hypersensitivity reactions.
HLA-B*1502
HLA-B*1502 is present at a frequency of more than 1% only in persons of Southeast Asian ancestry (Han Chinese, Thai, Malaysians, Indians).
Four meta-analyses of which two identical (with a total of 12, 17, 17 and 54 Asian SJS/TEN cases per meta-analysis), one case-control study with 28 Iranian SJS/TEN cases, and two pooled case-control studies with a total of 7 Han Chinese SJS/TEN cases showed that this allele increased the risk of lamotrigine-induced SJS/TEN (OR = 2.4-7.9, with the OR in the meta-analyses decreasing with increasing number of total SJS/TEN cases) (Deng 2018, Zeng 2015, Bloch 2014, Cheung 2013, Sabourirad 2021, and Hung 2010). A meta-analysis of two studies with a total of 7 Han Chinese SJS/TEN cases and four case-control studies with respectively 22, 7, 6, and 6 Chinese SJS/TEN cases, did not find an increased risk for HLA-B*1502 carriers (Sukasem 2021, Shi 2017, Kwan 2014, Wang 2014, and Hung 2010).
Although the evidence is not strong, the KNMP Pharmacogenetics Working Group considers the evidence to be sufficient to conclude that a gene-drug interaction is present. In addition, because life-threatening adverse events should be avoided if possible, even if both the incidence and the risk increase are low, the KNMP Pharmacogenetics Working Group decided that a warning is necessary (yes/yes-interaction).
An incidence of lamotrigine-induced SJS/TEN of 1 in 1000 users in combination with a 2.4-7.9 fold risk increase for HLA-B*1502 carriers, would result in a risk for HLA-B*1502 carriers of 0.24-0.79%. Because of the lack of reports of a higher incidence in children of carbamazepine-induced SJS/TEN, which has a much stronger association with HLA-B*1502 than lamotrigine-induced SJS/TEN, the reported high incidence of lamotrigine-induced serious adverse skin reactions in children is unlikely to concern HLA-B*1502-associated reactions. So, the incidence of lamotrigine-induced serious adverse skin reactions in HLA-B*1502 carriers is likely to be comparable between adult and paediatric users.
HLA-B*3801
Of the 3 case-control studies investigating the association with HLA-B*3801, one found an association with SJS/TEN (OR = 147) and with SJS/TEN/DRESS (OR = approx. 20) (Ramirez 2017; 3 Spanish SJS/TEN and 3 Spanish DRESS). The second found an association with SJS/TEN before, but not after correction for multiple comparisons (OR = 4.7) (Lonjou 2008; 19 European SJS/TEN cases) and the third did not find an association with severe cutaneous events (Kazeem 2009; 22 European cases (12 DRESS, 9 SJS, 1 TEN)). Because the case-control studies contradict each other with regard to size and significance of the effect, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.
HLA-A*2402
Of the four case-control studies investigating the association with HLA-A*2402, one found an association with SJS/TEN also after correction for 8 different HLA alleles (OR = 4.48) (Shi 2017; 22 Han Chinese SJS/TEN cases) and another found an association with DRESS (OR = 49), but not with SJS/TEN (Ramirez 2017; 3 Spanish SJS/TEN and 3 Spanish DRESS cases, no correction for multiple comparisons). The other two case-control studies with more than

5 cases of severe cutaneous adverse events did not find an association with SJS/TEN (Kim 2017; 18 Korean SJS/TEN cases) or with severe cutaneous adverse events (Kazeem 2009; 22 European cases (12 DRESS, 9 SJS, 1 TEN)). The meta-analysis of Deng 2018 of the two Asian studies (Shi 2017 and Kim 2017; total of 40 SJS/TEN cases) found an association between HLA-A*2402 and SJS/TEN (OR = 3.50). However, a meta-analysis of two studies is hardly a meta-analysis. In addition, Shi 2017 does not seem to be a very representative study, being the only study/meta-analysis with more than 7 Asian SJS/TEN cases that did not find an association between HLA-B*1502 and SJS/TEN. In addition, Kim 2017 found a significant association between HLA-A*3101 and SJS/TEN, but not between HLA-A*2402 and SJS/TEN, suggesting HLA-A*2402 to be of minor importance. Because the case-control studies contradict each other and the meta-analysis has clear limitations, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of this gene-drug combination in the electronic decision support systems and/or the KNMP Kennisbank.

HLA-A*3101 and HLA-B*4403

For both HLA-A*3101 and HLA-B*4403, one case-control study supported an association (Kim 2017 with 18 Korean SJS/TEN and Park 2016 with 7 Korean SJS/TEN, respectively), but another found no association for either allele (Kazeem 2009; 22 European cases (12 DRESS, 9 SJS, 1 TEN)). For this reason, the KNMP Pharmacogenetics Working Group decided that there was not enough evidence for gene-drug interactions and not enough cause for inclusion of these gene-drug combinations in the electronic decision support systems and/or the KNMP Kennisbank.

Other alleles

None of the case-control studies showed an association for the other alleles. Therefore, it was decided that there was not enough cause for inclusion of these gene-drug combinations in the KNMP Kennisbank.

For the included interaction between lamotrigine and HLA-B*1502, you can find an overview of the effects in the background information text of this gene-drug interaction in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

The justification for the therapeutic recommendation for this genotype group is provided below.

*Therapeutic recommendation for HLA-B*1502*

If an alternative is possible, choosing an alternative is recommended. If an alternative is not possible, it is recommended to advise the patient to report any rash immediately.

Carbamazepine is excluded as a possible alternative, because it increases the risk of severe cutaneous adverse events in these patients to a much higher extent than lamotrigine. For carbamazepine, positive predictive values for SJS/TEN of up to 7.7% have been calculated (Hung SI et al. HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine. Personalized Med 2005;2:225–37). For phenytoin, a similar increase in risk as for lamotrigine has been reported (OR = 3.5-4.3). For oxcarbazepine, a similar SJS/TEN risk in these patients has been reported as for phenytoin (calculated positive predictive values for SJS/TEN of respectively 0.73% and 0.65%) (Chen CB et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology 2017;88:78-86 and Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94), but the most severe forms (SJS/TEN-overlap and TEN) have not been observed for oxcarbazepine.

Recommendation concerning pre-emptive genotyping, including justification of choices:

HLA-B*1502 has not been detected in a sample of 1350 Dutch persons (Allele Frequency Net Database: http://www.allelefrequencies.net). For this reason, the KNMP Pharmacogenetics Working Group does not consider genotyping of Dutch patients in general before starting lamotrigine to be useful.

However, the HLA-B*1502 frequency is high in Asians, except for Japanese and Koreans. In Japanese the HLA-B*1502 frequency is very low (< 0.1%). In Korea, it is less than 1% in some populations and more than 1% in other populations, with a mean of approximately 2% according to the SmPC of carbamazepine. The KNMP Pharmacogenetics Working Group considers genotyping of patients of Asian descent other than Japanese descent before starting lamotrigine to be beneficial for drug safety. It is advised to consider genotyping these patients before (or directly after) drug therapy has been initiated to guide drug selection.

The clinical implication of the gene-drug interaction scores 4 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points) (see also the clinical implication score tables at the end of this risk analysis):

HLA-B*1502 has been shown to increase the risk of the severe and possibly life-threatening cutaneous adverse event SJS/TEN (code E corresponding to CTCAE grade 4). This results in 1 out of the maximum score of 2 points for the first criterion of the clinical implication score, the clinical effect associated with the gene-drug interaction (1 point for code D or E (CTCAE grade 3 or 4)).

Three meta-analyses (one of 7 and two of 4 case-control studies), a case-control study and a pooled analysis of 2 case-control studies showed that HLA-B*1502 increased the risk of lamotrigine-induced SJS/TEN. This results in the maximum of 3 points for the second criterion of the clinical implication score, the level of evidence supporting the associated clinical effect grade ≥ 3 (3 points for at least three publications with level of evidence score ≥ 3).

According to the SmPC Lamictal (lamotrigine) 26-01-22, the incidence of SJS/TEN is 1:1000 adult users and the incidence of DRESS < 1:10,000 adult users and the incidence of skin rash necessitating hospital admission is 0.3-1% in paediatric users. This indicates that even if HLA-B*1502 would have been the only cause of SJS/TEN in adult users, a minimum of 1000 patients would have to be genotyped to prevent one case of lamotrigine-induced SJS/TEN. Because of the lack of reports of a higher incidence in children of carbamazepine-induced SJS/TEN, which has a much stronger association with HLA-B*1502 than lamotrigine-induced SJS/TEN, the reported high incidence of lamotrigine-induced serious adverse skin reactions in children is unlikely to concern HLA-B*1502-associated reactions.

So, the incidence of lamotrigine-induced serious adverse skin reactions in HLA-B*1502 carriers is likely to be comparable between paediatric and adult users. Because the number needed to genotype to prevent 1 adverse event code ≥ D (grade ≥ 3) is larger than 1000, this results in 0 out of the maximum of 3 points for the third criterion of the clinical implication score, the number needed to genotype (NNG) to prevent one clinical effect code ≥ D (grade ≥ 3) (only points for NNG ≤ 1000).
The SmPC does not mention HLA-B*1502 or any other HLA allele. This results in 0 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (only points if at least one genotype is mentioned in the SmPC).

Source	Code	Effect	Comments
ref. 1 Sukasem C et al. Spectrum of cutaneous adverse reactions to aromatic antiepileptic drugs and human leukocyte antigen genotypes in Thai patients and meta-analysis. Pharmacogenomics J 2021;21:682-90. PMID: 34175889.	3 B*1502: AA	Meta-analysis of 2 case-control studies in Asians with carbamazepine-tolerant patients as controls. The studies included a total of 7 cases and 78 controls. Both studies were in Han Chinese. Of the 2 studies in this meta-analysis, 1 was included in this risk analysis separately (Cheung 2013). Of the 2 studies in this meta-analysis, 1 was included in the meta-analysis of Zeng 2015 (Man 2007), and the other one in the meta-analyses of Deng 2018, Bloch 2014 and Cheung 2013 (Cheung 2013). A random effects model was used for the meta-analysis, but prospective registration of the protocol was not mentioned. The search and selection strategy and the method of data extraction were not mentioned. Quality of the included studies was not assessed. Publication bias analysis was not performed. Results: Association between HLA-B*1502 and SJS/TEN: Trend for an increased risk (95% CI of the OR: 0.91-27.80) (NS) 43% of the cases and 14% of the controls had B*1502. There was no heterogeneity between the studies.	
ref. 2 Sabourirad S et al. Investigating the association of lamotrigine and phenytoin-induced Stevens-Johnson syndrome/ Toxic Epidermal Necrolysis with HLA-B*1502 in Iranian population. Exp Dermatol 2021;30:284-7. PMID: 33217035.	4 B*1502: E	In a case-control study, 28 Iranian cases with lamotrigine-induced SJS/TEN were compared to 25 lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without SJS/TEN after using lamotrigine for at least 2 months. Any medication other than lamotrigine in the past year was excluded. Results: Association between HLA-B*1502 and SJS/TEN: OR = 4.74 (95% CI: 1.14-19.73) (S), before logistic regression OR = 7.93 (95% CI: 1.49-42.14) (S), after logistic regression adjusting for age and sex 39% of the cases and 12% of the controls had B*1502. Cramer's V for the association was 0.309, indicating an moderate association.	Author's conclusion: "Lamotrigine-induced SJS/TEN is associated with HLA-B*1502 allele in an Iranian population."
ref. 3 Deng Y et al. Association between HLA alleles and lamotrigine-induced cutaneous adverse drug reactions in Asian populations: a meta-analysis. Seizure 2018;60:163-71. PMID: 30015149.	4	Meta-analysis of 11 case-control studies in Asians with lamotrigine-tolerant patients as controls. 8 of the studies investigated SJS/TEN, the other 3 only MPE. 8 of the studies were in Chinese, 2 in Koreans and 1 in Thai. Included studies had a score of 5-7 on the 9-item Newcastle-Ottawa scale for study quality. For HLA-B*1502, the meta-analysis included 7 studies with 54 cases and 313 controls for SJS/TEN, and 6 studies with 165 cases and 274 controls for MPE. For HLA-A*2402, the meta-analysis included 2 studies with 40 cases and 131 controls for SJS/TEN, and 2 studies with 76 cases and 131 controls for MPE. Of the 7 studies in the meta-analysis for HLA-B*1502 and SJS/TEN, 5 were included in this risk analysis separately (Shi 2017, Cheung 2013, Kwan 2014, Wang 2014 and	Author's conclusion: "In Asian populations, HLA-B*1502 is a risk factor for lamotrigine-induced bullous lesions such as SJS/TEN in Chinese populations, and HLA-A*2402 is associated with the susceptibility to either SJS/TEN or MPE."

<table>
<tr>
<td>ref. 3, continuation</td>
<td>B*1502: E

A*2402: E</td>
<td>Hung 2010).
Both studies in the meta-analysis for HLA-A*2402 and SJS/TEN were included in this risk analysis separately (Kim 2017 and Shi 2017).
Of the 7 studies in the meta-analysis for HLA-B*1502 and SJS/TEN, 2 were included in the meta-analyses of Bloch 2014 and Cheung 2013 (Cheung 2013 and Hung 2010), and 1 in the meta-analysis of Zeng 2015 (Hung 2010).
A fixed-effects model was used in case of absence of heterogeneity between the studies. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the method of data extraction was standardized.
Because of the limited number of studies in each meta-analysis, the fail-safe number with significance set at 0.05 (Nfs 0.05) for each meta-analysis was applied to analyse publication bias.

Results:
<table>
<tr><td colspan="2">Association between HLA alleles and SJS/TEN:</td></tr>
<tr><td>HLA allele</td><td></td></tr>
<tr><td rowspan="6">B*1502</td><td>OR = 2.4 (95% CI: 1.20-4.78) (S)</td></tr>
<tr><td>28% of cases and 13% of controls had B*1502.</td></tr>
<tr><td>Significance was lost when the meta-analysis was restricted to only two studies (one in Thai and one in Hongkong Chinese) by excluding the five studies in Han Chinese. However, exclusion of either the Thai or Hongkong Chinese study from the meta-analysis increased the P-value with respectively a factor of 2 and a factor of 3, suggesting these studies to contribute to the significance of the result.</td></tr>
<tr><td>Of the 7 studies included in the meta-analysis, the study by Shi 2017 suggested the smallest effect of B*1502 (OR = 1.28 versus OR = 2.44-10.00 for the other 6 studies).</td></tr>
<tr><td>No significant effect of B*1502 was found in the MPE meta-analysis.</td></tr>
<tr><td rowspan="3">A*2402</td><td>OR = 3.50 (95% CI: 1.61-7.59) (S)</td></tr>
<tr><td>53% of cases and 21% of controls had A*2402.</td></tr>
<tr><td>The MPE meta-analysis showed A*2402 to also increase the MPE risk (OR = 2.14 (95% CI: 1.10-4.16) (S)).</td></tr>
<tr><td colspan="2">No heterogeneity between the studies was observed in the meta-analyses.</td></tr>
<tr><td colspan="2">The fail-safe number values were elevated for B*1502 and A*2402 (18.9 and 6.1, respectively), suggesting that the associations based on the current data were reliable.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 4
Shi YW et al.
HLA-A*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions.
Neurology 2017;88:2183-2191.
PubMed PMID: 28476759.</td>
<td>4</td>
<td>In a case-control study, 22 southern Han Chinese cases with lamotrigine-induced SJS/TEN were compared to 102 lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without cutaneous adverse reactions after using lamotrigine for at least 3 months.
Co-medication associated with SJS/TEN was excluded. 10 cases used a nonaromatic anti-epileptic drug concomitantly and 1 case another aromatic anti-epileptic drug. The other aromatic anti-epileptic drug was started more than 2 months before lamotrigine.

Results:</td>
<td>Author’s conclusion:
”HLA-A*24:02 was associated significantly with Stevens-Johnson syndrome induced by the aromatic anti-epileptic drugs as a group and by individual drugs (carbamazepine,</td>
</tr>
</table>

ref. 4, continuation		Association between HLA alleles and SJS/TEN:				lamotrigine, phenytoin)."
		HLA allele	OR	95% CI	allele carrier frequency in the controls	
	A*2402: E	A*2402	4.48 S, also after Bonferroni correction for 8 HLA-A alleles The sensitivity of A*2402 to predict SJS was 45.4%, the specificity 84.3%. In a case-control study with 59 lamotrigine-induced maculopapular exanthema cases, no significant effect of A*2402 was found.	1.66-12.11	15.7%	
	B*5102: AA	B*5102	14.7 S, but NS after Bonferroni correction for 24 HLA-B alleles	1.46-148	0.0%	
	B*1502, A*0201, A*0203, A*0206, A*0207, A*1101, A*1153, A*3303, A*6801, B*0702, B*1301, B*1501, B*1512, B*3501, B*3505, B*3514, B*3802, B*4001, B*4446, B*4501, B*4601, B*4801, B*5101, B*5111, B*5201, B*5401, B*5502, B*5504, B*5601, B*5610, B*5801, C*0102, C*0302, C*0303, C*0304, C*0401, C*0403, C*0602, C*0702, C*0801, C*1202, C*1402,	B*1502	NS		18.6%	
		A*0201	NS		10.8%	
		A*0203	NS		14.7%	
		A*0206	NS		12.8%	
		A*0207	NS		27.5%	
		A*1101	NS		56.9%	
		A*1153	NS		1.1%	
		A*3303	NS		20.6%	
		A*6801	NS		0.0%	
		B*0702	NS		1.0%	
		B*1301	NS		23.5%	
		B*1501	NS		2.0%	
		B*1512	NS		1.0%	
		B*3501	NS		1.0%	
		B*3505	NS		2.0%	
		B*3514	NS		0.0%	
		B*3802	NS		3.9%	
		B*4001	NS		20.6%	
		B*4446	NS		0.0%	
		B*4501	NS		0.0%	
		B*4601	NS		29.4%	
		B*4801	NS		1.0%	
		B*5101	NS		8.8%	
		B*5111	NS		0.0%	
		B*5201	NS		1.0%	
		B*5401	NS		4.9%	
		B*5502	NS		3.9%	
		B*5504	NS		1.0%	
		B*5601	NS		0.0%	
		B*5610	NS		0.0%	
		B*5801	NS		17.7%	
		C*0102	NS		34.3%	
		C*0302	NS		21.6%	
		C*0303	NS		5.9%	
		C*0304	NS		26.5%	
		C*0401	NS		7.8%	
		C*0403	NS		3.9%	
		C*0602	NS		3.9%	
		C*0702	NS		27.5%	
		C*0801	NS		23.5%	
		C*0803	NS		0.0%	
		C*1202	NS		5.9%	
		C*1402	NS		9.8%	

<table>
<tr>
<td>ref. 4, continuation</td>
<td>C*1502, DRB1 *0301, *0405, *0406, *0410, *0701, *0803, *0901, *1101, *1201, *1202, *1405, *1454, *1501, *1502, *1602: AA</td>
<td>
<table>
<tr><td>C*1502</td><td>NS</td><td></td><td>4.9%</td></tr>
<tr><td>DRB1*0301</td><td>NS</td><td></td><td>13.9%</td></tr>
<tr><td>DRB1*0405</td><td>NS</td><td></td><td>11.9%</td></tr>
<tr><td>DRB1*0406</td><td>NS</td><td></td><td>2.0%</td></tr>
<tr><td>DRB1*0410</td><td>NS</td><td></td><td>1.0%</td></tr>
<tr><td>DRB1*0701</td><td>NS</td><td></td><td>5.9%</td></tr>
<tr><td>DRB1*0803</td><td>NS</td><td></td><td>5.9%</td></tr>
<tr><td>DRB1*0901</td><td>NS</td><td></td><td>27.7%</td></tr>
<tr><td>DRB1*1101</td><td>NS</td><td></td><td>8.9%</td></tr>
<tr><td>DRB1*1201</td><td>NS</td><td></td><td>5.9%</td></tr>
<tr><td>DRB1*1202</td><td>NS</td><td></td><td>21.8%</td></tr>
<tr><td>DRB1*1405</td><td>NS</td><td></td><td>5.9%</td></tr>
<tr><td>DRB1*1454</td><td>NS</td><td></td><td>11.9%</td></tr>
<tr><td>DRB1*1501</td><td>NS</td><td></td><td>20.8%</td></tr>
<tr><td>DRB1*1502</td><td>NS</td><td></td><td>9.9%</td></tr>
<tr><td>DRB1*1602</td><td>NS</td><td></td><td>15.8%</td></tr>
<tr><td colspan="4">HLA-C*0801 is located on the same haplotype as HLA-B*1502.</td></tr>
</table>

Note: HLA-A-, HLA-B-, HLA-C- and HLA-DRB1-variants were characterized. For all detected variants the association with SJS/TEN was investigated.
</td>
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</tr>
<tr>
<td>ref. 5
Kim BK et al.
HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population.
Ann Allergy Asthma Immunol 2017;118:629-630.
PubMed PMID: 28351624.</td>
<td>3

A*3101: E

Cw*0304 : AA

B*5201: AA

Cw*1202 : AA</td>
<td>
In a case-control study, 18 Korean cases with lamotrigine-induced SJS/TEN were compared to 29 lamotrigine-tolerant controls. In addition, a population control of 485 Korean persons was used.
Relevant co-medication was not excluded.
Bonferroni correction was for 64 comparisons (32 HLA-alleles and two control groups).

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN (cases compared to lamotrigine-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele frequency in the population controls</td></tr>
<tr><td rowspan="3">A*3101</td><td>11.43</td><td>1.95-59.77</td><td rowspan="3">5.4%</td></tr>
<tr><td colspan="2">S, but NS after Bonferroni correction</td></tr>
<tr><td colspan="2">Results were significant for cases compared to population controls (OR = 7.27, 95% CI: 2.63-18.45) (S, also after Bonferroni correction).</td></tr>
<tr><td rowspan="3">Cw*0304</td><td>0.09</td><td>0.01-0.83</td><td rowspan="3">6.9%</td></tr>
<tr><td colspan="2">S, but NS after Bonferroni correction</td></tr>
<tr><td colspan="2">Results were NS for cases compared to population controls.</td></tr>
<tr><td rowspan="3">B*5201</td><td colspan="2">trend for an increased risk (p = 0.063), but not after Bonferroni correction (NS).</td><td rowspan="3">2.8%</td></tr>
<tr><td colspan="2">Results were similar for cases compared to population controls (OR = 4.84, 95% CI: 1.49-15.73) (S, but NS after Bonferroni correction).</td></tr>
<tr><td rowspan="3">Cw*1202</td><td colspan="2">trend for an increased risk (p = 0.063), but not after Bonferroni correction (NS).</td><td rowspan="3">2.5%</td></tr>
<tr><td colspan="2">Results were similar for cases compared to population controls (OR = 5.49, 95% CI: 1.68-17.94) (S, but</td></tr>
</table>
</td>
<td>Author’s conclusion:
”We found evidence for a significant association between the HLA-A*31:01 allele and risk for lamotrigine-induced severe cutaneous adverse reactions in Korean patients.”</td>
</tr>
</table>

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<td>ref. 5, continuation</td>
<td></td>
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<table>
<tr><td></td><td>NS after Bonferroni correction).</td><td></td></tr>
<tr><td>Cw*0401</td><td>trend for an increased risk (p = 0.068), but not after Bonferroni correction (NS).</td><td>6.6%</td></tr>
<tr><td>Cw*0401 : AA</td><td>Results were similar for cases compared to population controls (OR = 3.41, 95% CI: 1.24-9.42) (S, but NS after Bonferroni correction).</td><td></td></tr>
<tr><td>B*1302</td><td>trend for an increased risk (p = 0.089), but not after Bonferroni correction (NS).</td><td>3.5%</td></tr>
<tr><td>B*1302: AA</td><td>Results were similar for cases compared to population controls (OR = 5.44, 95% CI: 1.82-16.23) (S, but NS after Bonferroni correction).</td><td></td></tr>
<tr><td>B*3503</td><td>NS, OR could not be determined (allele frequency is 0% in tolerant controls).</td><td>0.4%</td></tr>
<tr><td>B*3503: AA</td><td>Cases compared to population controls: OR = 15.03, 95% CI: 2.56-88.16 (S, but NS after Bonferroni correction).</td><td></td></tr>
<tr><td>B*5701</td><td>NS, OR could not be determined (allele frequency is 0% in tolerant controls).</td><td>0.2%</td></tr>
<tr><td>B*5701: AA</td><td>Cases compared to population controls: OR = 30.19, 95% CI: 3.99-228.05 (S, but NS after Bonferroni correction).</td><td></td></tr>
<tr><td>Cw*1203</td><td>NS, OR could not be determined (allele frequency is 0% in tolerant controls).</td><td>0.5%</td></tr>
<tr><td>Cw*1203 : AA</td><td>Cases compared to population controls: OR = 12.00, 95% CI: 2.16-66.60 (S, but NS after Bonferroni correction).</td><td></td></tr>
<tr><td>A*2402</td><td>NS</td><td>21.6%</td></tr>
<tr><td>A*2402: AA</td><td>Also NS for cases compared to population controls.</td><td></td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Ramírez E et al. Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population. Pharmacol Res 2017;115:168-178. PubMed PMID: 27888155.</td>
<td>3

B*3801: E</td>
<td>
In a case-control study, 6 Spanish White cases with lamotrigine-induced severe cutaneous adverse events (3 SJS/TEN and 3 DRESS) were compared to 10 lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without adverse events after using lamotrigine for at least 3 months. In addition, a Spanish population control of 253 persons was used.
Relevant co-medication was not excluded.
For the total group of antiepileptic drug induced cases with severe cutaneous adverse events (14 SJS/TEN and 12 DRESS), the sample size was calculated to detect a specified OR > 5, with a given power of 80%.

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN (cases compared to lamotrigine-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the population controls</td></tr>
<tr><td>B*3801</td><td>147.00 (S)</td><td>1.88–483</td><td>5.1%</td></tr>
<tr><td></td><td colspan="2">All 3 cases and none of the controls were B*3801-</td><td></td></tr>
</table>
</td>
<td>Author’s conclusion:
”We identified several significant genetic risk factors for the first time in the Spanish Caucasian population: HLA-B*38:01 for lamotrigine- and phenytoin-induced SJS/TEN, and HLA-A*24:02 for lamotrigine- and phenytoin-induced DRESS.”</td>
</tr>
</table>

ref. 6, continuation			carriers, indicating a positive and negative predictive value of 100%.		
	A*0101, A*0201, A*0301, A*1101, A*2601, A*6901, B*3508, B*4402, B*4901, Cw*0401, Cw*0701, Cw*0802, Cw*1203, Cw*1204/5 : AA		Results were similar for the comparison with the population controls (OR = 124.70; 95% CI: 6.78-77.76x10^6) (S).		
		A*0101	NS		19.8%
		A*0201	NS		52.6%
		A*0301	NS		18.6%
		A*1101	NS		15.0%
		A*2601	NS		1.6%
		A*6901	NS		0.0%
		B*3508	NS		1.2%
		B*4402	NS		8.7%
		B*4901	NS		5.1%
		Cw*0401	NS		27.7%
		Cw*0701	NS		28.5%
		Cw*1203	NS		13.4%
		Cw*1204/5	NS		0.0%
		Results for all severe cutaneous adverse events combined (SJS/TEN + DRESS) were similar, except for: - the ORs for B*3801 being a factor 7 smaller - a trend for an increased risk for B*1801 compared to tolerant controls (p = 0.086), but not compared to population controls (like is the case for DRESS cases (see below))			
		Association between HLA alleles and DRESS (cases compared to lamotrigine-tolerant controls):			
		HLA allele	OR	95% CI	allele carrier frequency in the population controls
	A*2402: E	A*2402	49.00 (S)	1.25-46.13x10^6	17.4%
			All 3 cases and 1 of the 10 controls were A*2402-carriers, indicating a positive predictive value of 100%.and a negative predictive value of 90%.		
			Results were similar for the comparison with the population controls (OR = 34.83; 95% CI: 2.03-209.71) (S).		
	B*1801: AA	B*1801	trend for an increased risk (p = 0.08) (NS)		18.2%
			Results were NS for cases compared to population controls.		
	B*0801, B*1501, B*2705, B*3905, Cw*0303, Cw*06/12, Cw*0702,	A*0101	NS		19.8%
		A*0201	NS		52.6%
		B*0801	NS		13.4%
		B*1501	NS		5.1%
		B*2705	NS		4.3%
		B*3905	NS		0.0%
		Cw*0303	NS		5.5%
		Cw*06/12	NS		-
		Cw*0701	NS		28.5%
		Cw*0702	NS		19.4%

ref. 6, continuation	Cw*1502 : AA	Cw*1502 | NS | | 4.7% Note: All HLA class I variants (HLA-A-, HLA-B- and HLA-C-variants) were characterized. For all variants in the cases, the association with severe cutaneous adverse event was investigated.	
ref. 7 Park HJ et al. HLA allele frequencies in 5802 Koreans: varied allele types associated with SJS/TEN according to culprit drugs. Yonsei Med J 2016;57:118-26. PubMed PMID: 26632391.	3 B*4403: E	Genotyping for HLA was performed in Korean patients to prepare for organ or stem cell transplantation because of hepatic failure, renal failure and hematologic malignancy or to diagnose specific HLA-associated diseases, such as Behcet's disease, ankylosing spondylitis and SJS/TEN. Of 25 lamotrigine users, 7 had SJS/TEN. The other 18 patients were used as tolerant controls. Relevant co-medication was not excluded. Results: Association between HLA-B*4403 and SJS/TEN (cases compared to tolerant controls (carrier frequency 5.6%)): OR = 12.75; 95% CI: 1.03-157.14 (S, but NS according to the p-value (0.053)) 42.9% of the cases was carrier of HLA-B*4403. The allele frequency of HLA-B*4403 in the total number of genotyped patients was 10.0%. This would correspond with a HLA-B*4403 carrier frequency of 19%. Note: The allele frequency of HLA-B*1502 was low (0.3%) in the total number of genotyped Korean patients.	Author's conclusion: "HLA-B*44:03 may be associated with lamotrigine-induced SJS/TEN."
ref. 8 Zeng T et al. Association of HLA-B*1502 allele with lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: a meta-analysis. Int J Dermatol 2015;54:488-93. PubMed PMID: 25428396.	4 B*1502: E	Meta-analysis of 4 case-control studies with lamotrigine-tolerant controls. The 4 studies included in total 12 SJS/TEN cases and 128 controls. All four studies were in Han Chinese. The four studies had a score of 5 or 6 on the 9-item Newcastle-Ottawa scale for study quality. Of the 4 studies in this meta-analysis, 1 was included in this risk analysis separately (Hung 2010). Of the 4 studies in this meta-analysis, 3 were included in the meta-analyses of Bloch 2014 and Cheung 2013 (An 2010, Hung 2010 and Shi 2011). In the absence of publication bias and heterogeneity between the studies, a fixed-effect model was used for the analysis. This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent and the method of data extraction was standardized. Publication bias was analysed with Begg's and Egger's test, but not by funnel plot. Results: Association between HLA-B*1502 and SJS/TEN (cases compared to lamotrigine-tolerant controls (carrier frequency 9.4%)): OR = 4.98; 95% CI: 1.43-17.28 (S) 33% of the cases was carrier of HLA-B*1502. There was no heterogeneity between the studies. There were no indications for publication bias.	Author's conclusion: "We found a statistical association between HLA-B*1502 and lamotrigine-induced SJS/TEN in Han Chinese subjects."
ref. 9 Kwan PK et al. Association between HLA-B*15:02 allele and antiepileptic drug-induced severe cutaneous reactions in Hong Kong Chinese: a population-based study. Hong Kong Med J 2014;20 Suppl 7:16-8.	3	In a case-control study, 6 Chinese cases with lamotrigine-induced SJS/TEN were compared to 30 age-matched lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without skin rash after using lamotrigine for at least 3 months. Co-medication that can induce SJS/TEN was not excluded. Based on estimation from previous results for antiepileptic drug induced SJS/TEN, the combined frequency of HLA-B*1502 was assumed to be 15% in controls and 49% in cases. A sample size of 55 cases and 275 controls was calculated to have 90% power to detect a difference in HLA-B*1502 frequency between cases and controls at	Author's conclusion: "HLA-B*15:02 was also found in 33.3% (2/6) of lamotrigine-induced SJS/TEN."

PMID: 25647819. **ref. 9, continuation**	B*1502: AA	P=0.001. To account for multiple comparisons, a P value of <0.001 after Bonferroni correction was considered statistically significant. Results: Association between HLA-B*1502 and SJS/TEN: NS before and after correction for multiple comparisons. 33% of the cases and 13% of the controls had B*1502. An association with lamotrigine-induced SJS/TEN was not found for the other 13 investigated HLA-B alleles either. These 13 HLA-B alleles were B*1301, B*1501, B*1525, B*3501, B*3802, B*4001, B*4601, B*5101, B*5102, B*5401, B*5502, B*5601, and B*5801.	
ref. 10 Wang W et al. Genetic predictors of Stevens-Johnson syndrome and toxic epidermal necrolysis induced by aromatic antiepileptic drugs among the Chinese Han population. Epilepsy Behav 2014;37:16-9. PMID: 24949577.	3 B*1502: AA	In a case-control study, 7 Han Chinese cases with lamotrigine-induced SJS/TEN were compared to 13 lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without an allergic reaction after using lamotrigine for at least 3 months. Co-medication with other antiepileptic drugs was excluded, but co-medication with other drugs that can induce SJS/TEN was not. Bonferroni's correction for multiple comparisons was used to adjust for the four antiepileptic drugs investigated. Results: Association between HLA-B*1502 and SJS/TEN: NS before and after correction for multiple comparisons. 29% of the cases and 8% of the controls had B*1502. An association with lamotrigine-induced SJS/TEN was not found for the other 4 investigated HLA alleles either. The other investigated HLA alleles were HLA-A, HLA-B or HLA-DRB1 alleles that showed a significantly higher or lower carrier or allele frequency in SJS/TEN cases compared to tolerant controls for all antiepileptic drugs together. These 4 HLA alleles were A*3301, B*5801, DRB1*0301, and DRB1*1501. B*5801 and DRB1*0301 were not found in the lamotrigine cases and tolerant controls.	Author's conclusion: "We did not detect a significant association between HLA-B*1502 and SJS/TEN induced by lamotrigine."
ref. 11 Bloch KM et al. Pharmacogenetics of antiepileptic drug-induced hypersensitivity. Pharmacogenomics 2014;15:857-68. PubMed PMID: 24897291.	3 B*1502: E	Meta-analysis of 4 case-control studies with lamotrigine-tolerant controls. The 4 studies included in total 17 SJS/TEN cases and 146 controls. All four studies were in Han Chinese. Of the 4 studies in this meta-analysis, 2 were included in this risk analysis separately (Cheung 2013 and Hung 2010). This meta-analysis included the same 4 studies as the meta-analysis of Cheung 2013. A fixed-effect model was used for the analysis, whereas a random effects model should be chosen when presence of heterogeneity cannot be excluded. The search strategy was specified, but the selection strategy and the method of data extraction were not. Quality of the included studies was not assessed. Publication bias analysis was not performed. Results: Association between HLA-B*1502 and SJS/TEN (cases compared to lamotrigine-tolerant controls (carrier frequency 10%)): OR = 3.59; 95% CI: 1.15-11.22 (S) 29% of the cases was carrier of HLA-B*1502. There was no heterogeneity between the studies.	Author's conclusion: "HLA-B*15:02 was associated with carbamazepine, lamotrigine and phenytoin-induced Stevens–Johnson syndrome in Asian populations indicating that pre-treatment testing may prevent cross-reactivity."
ref. 12 Cheung YK et al. HLA-B alleles asso-	3	A case-control study and a meta-analysis were performed. In the case-control study, 6 Han Chinese cases with lamotrigine-induced SJS/TEN were compared to 30 lamotrigine-	Author's conclusion: "Meta-analyses

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<td>ciated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia 2013;54:1307-14. PubMed PMID: 23692434.

ref. 12, continuation</td>
<td>B*1502: E</td>
<td>tolerant controls. Lamotrigine-tolerant controls were defined as patients without cutaneous adverse events after using lamotrigine for at least 3 months.
Relevant co-medication was not excluded.
Meta-analysis of 4 case-control studies with Han Chinese patients, SJS/TEN cases and lamotrigine-tolerant controls, including the case-control study in this article. The 4 studies included in total 17 cases and 146 controls.
Two of the four studies in this meta-analysis, were included in this risk analysis separately (Cheung 2013 (see above) and Hung 2010).
A fixed-effect model was used for the analysis (no heterogeneity between the studies). This indicates that the statistical method was chosen afterwards. The search and selection strategy was transparent, but the method of data extraction was not specified.
Quality of the included studies was not assessed.
Publication bias analysis was not performed.

Results:
<table>
<tr><td colspan="3">Association between HLA-B*1502 and SJS/TEN (cases compared to lamotrigine-tolerant controls):</td></tr>
<tr><td></td><td></td><td>B*1502 carrier frequency in the tolerant controls</td></tr>
<tr><td>case-control study</td><td>NS</td><td>13.3%</td></tr>
<tr><td rowspan="3">meta-analysis</td><td>OR = 3.59; 95% CI: 1.15-11.22 (S)</td><td rowspan="3">10.3%</td></tr>
<tr><td>There was no heterogeneity between the studies.</td></tr>
<tr><td>The sensitivity of B*1502 to predict SJS/TEN was 29%, the specificity 90%.</td></tr>
</table>
</td>
<td>showed a strong association of HLA-B*15:02 with phenytoin-SJS/ TEN and, to a lesser extent, lamotrigine-SJS/TEN.”</td>
</tr>
<tr>
<td>ref. 13
Hung SI et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349-56. PubMed PMID: 20235791.</td>
<td>3</td>
<td>In a case-control study, 6 Han Chinese cases with lamotrigine-induced SJS were compared to 67 lamotrigine-tolerant controls. Lamotrigine-tolerant controls were defined as patients without adverse events after using lamotrigine for more than 3 months.
Relevant co-medication was not excluded.
Given that 8% of controls carry the risk allele as reported in previous studies, a sample of 26 cases (phenytoin study) and 6 cases (lamotrigine study), 60 controls each will reach 90% power if 80% of the cases carry the risk allele.

Results:
<table>
<tr><td colspan="3">Association between HLA-B alleles and SJS (cases compared to lamotrigine-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td></td><td>allele carrier frequency in the tolerant controls</td></tr>
<tr><td rowspan="3">B*1502</td><td>NS</td><td rowspan="3">9%</td></tr>
<tr><td>33% of the cases was carrier of HLA-B*1502.</td></tr>
<tr><td>After combining the results of this study with the results of Man 2007, who found 1 Han Chinese patient with lamotrigine-induced SJS/TEN, who was a carrier of HLA-B*1502, the association was significant:</td></tr>
</table>
</td>
<td>Author’s conclusion:
”We suggest that aromatic antiepileptic drugs, including carbamazepine, oxcarbazepine and phenytoin, should be avoided in the B*1502 carrier and caution should also be exercised for lamotrigine.”</td>
</tr>
</table>

<table>
<tr>
<td>ref. 13, continuation</td>
<td>B*1502: E

B*5801: AA

B*38 variant: AA</td>
<td>
<table>
<tr><td></td><td>OR = 7.62; 95% CI: 1.4-42.4 (S)
with 43% of cases being carrier of HLA-B*1502</td><td></td></tr>
<tr><td>B*5801</td><td>NS
33% of the cases was carrier of HLA-B*5801.</td><td>14% (phenytoine-tolerant controls)</td></tr>
<tr><td>B*38 variant</td><td>None of the 6 cases carried a B*38 variant. However, B*3801 was not detected in 113 phenytoin tolerant controls, only B*3802 (10.6%)</td><td></td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 14
Kazeem GR et al. High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. Pharmacogenet Genomics 2009;19:661-5. PubMed PMID: 19668019.</td>
<td>3

A*6801:</td>
<td>
In a case-control study, 22 European cases with lamotrigine-induced severe cutaneous adverse events (12 DRESS, 9 SJS, 1 TEN) were compared to 43 lamotrigine-tolerant controls. Cases and controls were derived from a phase III clinical trial, in which patients with epilepsy were treated with lamotrigine. In addition, a European population control was used (data from the dbMHC database). Two cases (African and Hispanic) and three controls (2 Africans, 1 Hispanic) were of non-European ancestry. SJS/TEN was defined as a rash involving two or more mucous membranes and one of more of the following: fever, lymphadenopathy, hepatic dysfunction, haematological dysfunction, or renal dysfunction. DRESS was defined as rash associated with two more of the following: fever, lymphadenopathy, splenomegaly, hepatic dysfunction, renal dysfunction, myocarditis, or myoglobinuria. Lamotrigine-tolerant controls were defined as patients without any severe cutaneous adverse event symptoms after using lamotrigine for more than 8 weeks.
Relevant co-medication was not excluded, but cases and controls were matched for concomitant valproic acid use. In addition, considering their participation in a phase III clinical trial, co-medication of the patients should have been strictly controlled.
The Bonferroni method was used to correct for 112 different alleles and 4 different tests (lamotrigine-tolerant and population controls, and comparisons for all severe cutaneous adverse events and for DRESS only) (significance for $p < 0.0001$) or for 77 different allele clusters (based on the number of independent linkage disequilibrium clusters of the alleles) and 4 different tests (significance for $p < 0.00016$).
The study had approximately 80% statistical power to detect an effect size of 56 (genotype relative risk) for alleles with a frequency of 1%, assuming a disease prevalence of 0.0003 and a type 1 error rate (α) of 0.0001. The study had approximately 99% statistical power to detect a marker with effect size similar to the association observed between B*1502 and carbamazepine-induced SJS in Han Chinese (an odds ratio of 2504).

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and severe cutaneous adverse events (cases compared to lamotrigine-tolerant controls):</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele frequency in the population controls</td></tr>
<tr><td>A*6801</td><td>19.2
S, but NS after Bonferroni correction.</td><td>1.01-365</td><td>2.9%</td></tr>
</table>
</td>
<td>Author’s conclusion:
”No single major HLA-related genetic risk factor was identified for lamotrigine-induced severe cutaneous adverse reactions in patients of European origin. Only suggestive evidence was obtained for B*5801, A*6801, Cw*0718, DQB1*0609, and DRB1*1301.”</td>
</tr>
</table>

ref. 14, continuation	AA B*5801: AA C*1718: AA DQB1 *0609: AA DRB1 *1301: AA			Results were similar for the comparison with the population control: OR = 3.32; 95% CI: 1.17-9.44 (S, but NS after Bonferroni correction).			
				Both cases with A*6801 were of non-European origin (1 of African origin and 1 of Hispanic origin). However, the A*6801 allele frequencies in these populations are similar to that in the European population (2.2% and 2.6% respectively).			
		B*5801	14.6	0.74-289	0.8%		
			S according to p-value, but not according to 95% CI. NS after Bonferroni correction.				
			Results were similar for the comparison with the population control: OR = 9.45; 95% CI: 2.76-32.3 (S, but NS after Bonferroni correction).				
			Results were similar for the association with DRESS (S, but NS after Bonferroni correction).				
		C*1718	14.6	0.74-289	-		
			S according to p-value, but not according to 95% CI. NS after Bonferroni correction.				
			The allele frequency in the population control was not determined.				
		DQB1*0609	14.6	0.74-289	1.2%		
			S according to p-value, but not according to 95% CI. NS after Bonferroni correction.				
			Results were similar for the comparison with the population control: OR = 5.80; 95% CI: 1.40-24.0 (S, but NS after Bonferroni correction).				
		Linkage disequilibrium was observed between B*5801, C*1718 and DQB1*0609.					
		DRB1*1301	8.50	0.79-423	4.5%		
			S according to p-value, but not according to 95% CI. NS after Bonferroni correction.				
			Results were NS for the comparison with the population control.				
		No association was found for the following HLA alleles, which were present in the cases:					
		A*0101	A*0201	A*0202	A*0205		
		A*0301	A*1101	A*2301	A*2402		
		A*2902	A*3001	A*3101	A*3201		
		A*6601	B*0702	B*0801	B*1402		

<table>
<tr>
<td>ref. 14, continuation</td>
<td>85 alleles, indicated on the right: AA</td>
<td>
<table>
<tr><td>B*1501</td><td>B*1801</td><td>B*2705</td><td>B*3501</td></tr>
<tr><td>B*3502</td><td>B*3503</td><td>B*3801</td><td>B*4001</td></tr>
<tr><td>B*4101</td><td>B*4102</td><td>B*4402</td><td>B*4403</td></tr>
<tr><td>B*5101</td><td>B*5501</td><td>B*5701</td><td>C*0102</td></tr>
<tr><td>C*0202</td><td>C*0303</td><td>C*0304</td><td>C*0401</td></tr>
<tr><td>C*0401</td><td>C*0501</td><td>C*0602</td><td>C*0701</td></tr>
<tr><td>C*0702</td><td>C*0704</td><td>C*0802</td><td>C*1203</td></tr>
<tr><td>C*1402</td><td>C*1502</td><td>C*1601</td><td>C*1701</td></tr>
<tr><td>C*1703</td><td>DQB1*0201</td><td>DQB1*0202</td><td>DQB1*0301</td></tr>
<tr><td>DQB1*0302</td><td>DQB1*0303</td><td>DQB1*0402</td><td>DQB1*0501</td></tr>
<tr><td>DQB1*0503</td><td colspan="3">DQB1*0501/0502/0503/0504/0505</td></tr>
<tr><td>DQB1*0602</td><td>DQB1*0701</td><td>DQB1*0702</td><td>DQB1*0704</td></tr>
<tr><td>DQB1*0802</td><td>DQB1*1203</td><td>DQB1*1402</td><td>DQB1*1502</td></tr>
<tr><td>DQB1*1601</td><td>DQB1*1701</td><td>DQB1*1703</td><td>DRB1*0101</td></tr>
<tr><td>DRB1*0301</td><td>DRB1*0401</td><td>DRB1*0402</td><td>DRB1*0403</td></tr>
<tr><td>DRB1*0701</td><td>DRB1*0801</td><td>DRB1*0804</td><td>DRB1*1101</td></tr>
<tr><td>DRB1*1101</td><td>DRB1*1104</td><td colspan="2">DRB1*1201/1206/1210</td></tr>
<tr><td>DRB1*1302</td><td>DRB1*1303</td><td colspan="2">DRB1*1401/1454</td></tr>
<tr><td>DRB1*1501</td><td></td><td></td><td></td></tr>
</table>
Note: HLA-A, HLA-B, HLA-C, HLA-DQB1 and HLA-DRB1 alleles were determined. The association with severe cutaneous adverse events was investigated for all 112 HLA alleles.
</td>
<td></td>
</tr>
<tr>
<td>ref. 15
Lonjou C et al.
A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs.
Pharmacogenet Genomics 2008;18:99-107.
PubMed PMID: 18192896.</td>
<td>3

B*38: E

B*3801: AA

B*5101: AA
B*15: AA

12 alleles, indicated on the right: AA</td>
<td>
In a case-control study, HLA-B frequencies in 19 European cases with lamotrigine-induced SJS/TEN (11x SJS, 4x SJS/ TEN and 4x TEN) were compared with the frequencies in a mixed Western European population from a database. Of the cases, 18 were of European ancestry and 1 of African ancestry. Most association data were obtained from 17 cases of European ancestry.
Co-medication conferring a high SJS/TEN risk was excluded, but other co-medication was not.
The Bonferroni method was used to correct for 27 comparisons (27 different HLA-alleles; significance if p < 0.0018).

Results:
<table>
<tr><td colspan="4">Association between HLA alleles and SJS/TEN:</td></tr>
<tr><td>HLA allele</td><td>OR</td><td>95% CI</td><td>allele carrier frequency in the population controls</td></tr>
<tr><td rowspan="2">B*38</td><td>6.8</td><td>2.2-21</td><td rowspan="2">4.3%</td></tr>
<tr><td colspan="2">S, also after Bonferroni correction</td></tr>
<tr><td rowspan="2">B*3801</td><td>4.7</td><td>1.3-16</td><td rowspan="2">4.3%</td></tr>
<tr><td colspan="2">S, but NS after Bonferroni correction</td></tr>
<tr><td>B*3811</td><td colspan="2">Could not be determined, allele not determined in population control.</td><td>-</td></tr>
<tr><td>B*5101</td><td colspan="2">S, but NS after Bonferroni correction</td><td></td></tr>
<tr><td>B*15</td><td colspan="2">NS after Bonferroni correction</td><td>approx. 12%</td></tr>
<tr><td colspan="4">No association was found for the following HLA-B alleles, which were present in the cases:</td></tr>
<tr><td colspan="4">
<table>
<tr><td>B*07</td><td>B*08</td><td>B*13</td><td>B*18</td><td>B*27</td><td>B*35</td></tr>
<tr><td>B*39</td><td>B*44</td><td>B*53</td><td>B*57</td><td>B*39</td><td>B*39</td></tr>
</table>
</td></tr>
</table>
Note: All HLA-B alleles in the cases were determined in low resolution (two digits), selected HLA-B alleles were determined in high resolution (four digits).
</td>
<td>Author’s conclusion:
‘We also observed a significant association with B*38 for patients related to lamotrigine. The associated allele was infrequent; however, the OR as well as the statistical power of borderline efficacy to assure a true relationship were low. When we looked at subgroups defined by high-resolution genotyping there was no significant association with any subtype of B*38.’</td>
</tr>
</table>

Risk group	-

Comments:

- We only included studies with more than 5 cases with severe cutaneous adverse events in the risk analysis. Other articles did not contribute enough to the evidence to be included. There were no studies and case reports investigating possible alternatives and no studies on genotype-guided therapy.
  The article of Li 2020 (Li W et al. HLA-A*24:02 associated with lamotrigine-induced cutaneous adverse drug reactions: A systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e23929. PMID: 33350798) was not included in the risk analysis, because only 40 of the 187 cases in the meta-analysis with tolerant controls and 18 of the 110 cases in the meta-analysis with population controls had severe cutaneous adverse events.
  The article of Ihtisham 2019 (Ihtisham K et al. Association of cutaneous adverse drug reactions due to anti-epileptic drugs with HLA alleles in a North Indian population. Seizure 2019;66:99-103. PMID: 30826555) was not included in the risk analysis, because the 2 SJS/TEN and 4 DRESS cases were only analysed separately, resulting in less than 5 cases per case-control comparison.

Date of the literature search: 14 February 2022.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working group decision	HLA-B*1502	4 E	yes	yes	23 May 2022

Mechanism:

Although the mechanism of hypersensitivity for lamotrigine is not exactly known, analogy with other drug-hypersensitive reactions suggests the mechanism described below.
A cellular immune reaction against tissue cells is induced if peptides derived from proteins within these tissue cells bind to specific HLA proteins, are transported to the cell surface and are ”recognised” as foreign by specific immune cell proteins (T-cell receptors). Lamotrigine binds to either the cellular proteins or derived peptides, to specific HLA proteins or to specific T-cell receptors, thus inducing an interaction between an HLA peptide complex and a T-cell receptor, resulting in a cellular immune reaction against tissue cells.

Clinical Implication Score:

Table 1: Definitions of the available Clinical Implication Scores

Potentially beneficial	PGx testing for this gene-drug pair is potentially beneficial. Genotyping can be considered on an individual patient basis. If, however, the genotype is available, the DPWG recommends adhering to the gene-drug guideline	0-2 +
Beneficial	PGx testing for this gene-drug pair is beneficial. It is advised to consider genotyping the patient before (or directly after) drug therapy has been initiated to guide drug and dose selection	3-5 +
Essential	PGx testing for this gene-drug pair is essential for drug safety or efficacy. Genotyping must be performed before drug therapy has been initiated to guide drug and dose selection	6-10 +

Table 2: Criteria on which the attribution of Clinical Implication Score is based

Clinical Implication Score Criteria	**Possible Score**	**Given Score**
Clinical effect associated with gene-drug interaction (drug- or diminished efficacy-induced)		
• CTCAE Grade 3 or 4 (clinical effect score D or E)	+	+
• CTCAE Grade 5 (clinical effect score F)	++	
Level of evidence supporting the associated clinical effect grade ≥ 3		
• One study with level of evidence score ≥ 3	+	
• Two studies with level of evidence score ≥ 3	++	
• Three or more studies with level of evidence score ≥ 3	+++	+++
Number needed to genotype (NNG) in the Dutch population to prevent one clinical effect grade ≥ 3		
• 100 < NNG ≤ 1000	+	
• 10 < NNG ≤ 100	++	
• NNG ≤ 10	+++	
PGx information in the Summary of Product Characteristics (SmPC)		
• At least one genotype/phenotype mentioned	+	

OR • Recommendation to genotype OR • At least one genotype/phenotype mentioned as a contra-indication in the corresponding section	++ ++	
Total Score:	10+	4+
Corresponding Clinical Implication Score:		Beneficial