HLA: oxcarbazepine 6931

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, MPE = maculopapular exanthema, NS = not significant, OR = odds ratio, RR = relative risk, 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:
Oxcarbazepine can induce the severe and possibly life-threatening cutaneous adverse events SJS/TEN and DRESS. According to the SmPC of oxcarbazepine, the incidence of SJS/TEN is estimated to be less than 0.01% of users, while the incidence of DRESS is estimated to be between 0.01% and 0.1% of users. In Taiwan, the incidence of oxcarbazepine-induced SJS was calculated to be 0.08% of new users. Oxcarbazepine 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 oxcarbazepine.
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).
Two case-control studies (with respectively 20 and 3 SJS cases) and a meta-analysis of the largest case-control study and a case report showed that this allele increased the risk of oxcarbazepine-induced SJS (OR = 26-81, with the OR decreasing with increasing number of cases investigated) (Chen 2017, Hung 2010 and Tangamornsuksan 2018). In addition, 4 of the 7 Asian SJS cases were carrier of HLA-B*1502 (Sukasem 2021, Sun 2014, Wal 2011, Shankarkumar 2009, Lin 2009). Oxcarbazepine induced SJS/TEN seemed to be somewhat less severe than SJS/TEN induced by other aromatic antiepileptic drugs. The specified cases all concerned SJS. Descriptions of cases with TEN or with SJS/TEN-overlap were lacking.
A meta-analysis of 3 case-control studies with 23 SJS cases and 6 DRESS cases showed HLA-B*1502 to increase the risk of SJS or DRESS (OR = 18) (Liu 2018). The relatively low OR in this study might be due to the inclusion of DRESS cases. Chen 2017 did not find an association between DRESS and HLA-B*1502 in these 6 DRESS cases.
A retrospective cohort study including two cases with severe cutaneous adverse reactions (defined as toxic maculopapular eruption, acute generalized exanthematous pustulosis (AGEP), SJS, TEN, or DRESS), did not find being a carrier of HLA-B*1501 and/or HLA-A*3101 to significantly increase severe cutaneous adverse reaction risk (Lee 2022). The frequency of HLA-B*1502 and/or HLA-A*3101 in the patients in this study was 8,8%.
An Asian case with oxcarbazepine-induced pure cervical lymphadenopathy was HLA-B*1502 carrier (Liu 2021).
Although the evidence is not very strong, the KNMP Pharmacogenetics Working Group considers the evidence to be sufficient to conclude that a gene-drug interaction is present. In addition, because severe adverse events requiring hospitalisation should be avoided if possible, even if the incidence is low, the KNMP Pharmacogenetics Working Group decided that a warning is necessary (yes/yes-interaction).
The positive predictive value of HLA-B*1502 for the development of oxcarbazepine-induced SJS was calculated to be 0.73% (Chen 2017).
HLA-B*1518 and HLA-B*4001
The combined genotype HLA-B*1518/ HLA-B*4001 was found in two cases (Lin 2009 and Wal 2011). However, an association with one or both of these HLA-variants was not proven. The KNMP Pharmacogenetics Working Group decided that there was not enough evidence for a gene-drug interaction and not enough cause for inclusion of these gene-drug combinations in the electronic decision support systems and/or the KNMP Kennisbank.
HLA-A*3101
Except for one case report, there are no indications for an association of HLA-A*3101 with oxcarbazepine-induced severe cutaneous adverse events. A case-control study with 17 Taiwanese and 3 Thai SJS cases and 6 Taiwanese DRESS cases found no association of HLA-A*3101 with either SJS or DRESS (Chen 2017). Amstutz 2013 did not find HLA-A*3101 in 2 Canadian cases with oxcarbazepine-induced SJS. Kim 2018 reports a case of oxcarbazepine-induced DRESS in a paediatric HLA-A*3101 carrier. A retrospective cohort study including two cases with severe

cutaneous adverse reactions (defined as toxic maculopapular eruption, acute generalized exanthematous pustulosis (AGEP), SJS, TEN, or DRESS), did not find being a carrier of HLA-B*1501 and/or HLA-A*3101 to significantly increase severe cutaneous adverse reaction risk (Lee 2022). The frequency of HLA-B*1502 and/or HLA-A*3101 in the patients in this study was 8,8%. 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.
For the included interaction between oxcarbazepine 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 the incidence of carbamazepine-induced SJS/TEN in these patients is 10 times the incidence of oxcarbazepine-induced SJS/TEN (positive predictive values of 7.7% for carbamazepine and 0.73% for oxcarbazepine 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, and Chen 2017). In addition, carbamazepine-induced SJS/TEN seemed to be more severe than oxcarbazepine-induced SJS/TEN. For carbamazepine also cases of TEN and SJS/TEN-overlap were reported.
Phenytoin and lamotrigine are not recommended as alternatives. For these drugs, HLA-B*1502 has been reported to result in a similar increase in the risk of SJS/TEN (OR = 3.5-4.3 for phenytoin and OR = 2.4-7.9 for lamotrigine). The cost-effectiveness study of Chen 2016 calculated the positive predictive value of HLA-B*1502 for phenytoin-induced SJS/TEN to be 0.65%, which is similar to that of oxcarbazepine-induced SJS/TEN (Chen Z et al. Real-world cost-effectiveness of pharmacogenetic screening for epilepsy treatment. Neurology 2016;86:1086-94. PubMed PMID: 26888992). However, both for phenytoin and lamotrigine, also cases of TEN and SJS/TEN-overlap were reported.

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 oxcarbazepine 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 oxcarbazepine 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 5 out of the maximum of 10 points (with pre-emptive genotyping considered to be beneficial for scores ranging from 3 to 5 points):
HLA-B*1502 has been shown to increase the risk of the severe cutaneous adverse event SJS (code D corresponding to CTCAE grade 3). 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)).
Two case-control studies and two meta-analyses, one of a case-control study and a case report and one of three case-control studies, showed that HLA-B*1502 increased the risk of oxcarbazepine-induced SJS or SJS/TEN and DRESS. Because the largest meta-analysis was based on three case-control studies, there were 3 case-control studies adding to the evidence. 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).
In Taiwan, the incidence of oxcarbazepine-induced SJS was calculated to be 8.3 per 10,000 new users. Thus, even if HLA-B*1502 would be the only cause of SJS, more than 1200 patients would have to be genotyped to prevent one case of oxcarbazepine-induced SJS. 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 of oxcarbazepine contains a warning that HLA-B*1502 might increase the risk of SJS/TEN, but neither mentions HLA-B*1502 as a contra-indication for oxcarbazepine nor provides a consistent recommendation for pre-emptive genotyping (only indicating that, if possible, Han Chinese and Thai individuals should be screened for HLA-B*1502 before starting treatment with carbamazepine or a chemically related active substance, and that genetic screening for the presence of HLA-B*1502 can be considered for patients from risk populations (i.e. populations with a high HLA-B*1502 prevalence)). This results in 1 out of the maximum of 2 points for the fourth and last criterion of the clinical implication score, the pharmacogenetics information in the SmPC (1 point for at least one genotype/phenotype mentioned in the SmPC, but not mentioned as a contra-indication and no recommendation to genotype).

Source	Code	Effect	Comments
ref. 1 Lee KH et al. Reducing severe cutaneous adverse and type B adverse drug reactions using pre-stored human leukocyte antigen genotypes. Clin Transl Allergy 2022;12:e12098. PMID: 35070271.	3 B*1502 and/or A*3101: AA	By combining HLA-data from a transplantation data base with electronic health records, 171 South Korean patients with known HLA-A and HLA-B alleles that had used oxcarbazepine were identified. HLA alleles had not been taken into account during oxcarbazepine therapy. The frequency of HLA-B*1502 and/or HLA-A*3101 in the patients was 8,8%. 2 of the patients developed a severe cutaneous adverse reaction. Severe cutaneous adverse reactions included toxic maculopapular eruption, acute generalized exanthematous pustulosis (AGEP), SJS, TEN, and DRESS. Relevant co-medication was not excluded. Results: Incidence of severe cutaneous adverse reactions in patients with HLA-B*1502 and/or HLA-A*3101 compared to patients without HLA-B*1502 and/or HLA-A*3101 (incidence 0.6%): x 10.4 (NS) The incidence was 6.7% in carriers of HLA-B*1502 and/or HLA-A*3101. 50% of the cases was carrier of HLA-B*1502 and/or HLA-A*3101. Note: When both mild/moderate and serious type B reactions were investigated (a total of 17 cases), the authors claim to find a significantly increased risk in carriers of HLA-B*1502 and/or HLA-A*3101 despite the 95% confidence incidence interval of the OR suggesting the contrary (OR = 3.95 (95% CI: 0.80–16.01), p = 0.046).	Author's conclusion: "Higher risks of type B adverse drug reactions and severe cutaneous adverse reactions were observed in patients taking carbamazepine or oxcarbazepine if they had one of HLA-A*31:01, HLA-B*15:02, or HLA-B*15:11 alleles."
ref. 2 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.	1 B*1502: D	3 Thai patients with oxcarbazepine-induced SJS/TEN were identified. 2 of these patients (67%) were HLA-B*1502 carrier, which is 4.4 fold higher than the carrier frequency of 15% in the general population (470 genotyped Thai) (significance not determined).	Author's conclusion: "It bears noting that the HLA-B*15:02 allele frequency was higher (66.67%) in oxcarbazepine-induced cutaneous adverse drug reactions, although the patient samples were too small to draw any definitive conclusions."
ref. 3 Liu H et al. Association of the HLA-B*15:02 allele with pure cervical lymphadenopathy induced by carbamazepine and oxcarbazepine: a case report and literature review. Basic Clin Pharmacol Toxicol 2021;128:348-51. PMID: 32937013.	2 B*1502: C	An 16 year old Chinese boy developed cervical lymphadenopathy (bilaterally swollen neck without fever, itching or pain, due to enlarged lymph nodes) 3 months after starting oxcarbazepine 750 mg/day. He was HLA-B*1502-positive. The patient tested negative for five viruses and toxoplasma. After switching from oxcarbazepine to valproic acid, cervical lymphadenopathy completely regressed within six months without any treatment. The Naranjo probability score was 9, suggesting that oxcarbazepine was the cause of cervical lymphadenopathy. Lymphadenopathy can be one of the signs of DRESS, but the patient did not develop any other signs. 14 months earlier, he developed cervical lymphadenopathy on carbamazepine, which was completely resolved 5 months before starting oxcarbazepine.	Author's conclusion: "In our case, HLA-B*15:02 genotype might be a possible risk predictor for carbamazepine- and oxcarbazepine-induced lymphadenopathy. However, further investigation must be done."
ref. 4 Liu Y et al. Association between HLA-B*15:02 and oxcarbazepine-indu-	3	Meta-analysis of 4 case-control studies with oxcarbazepine-tolerant and/or population controls. 2 studies included both tolerant and population controls, 1 only tolerant controls and 1 only population controls. Only studies in populations with a HLA-B*1502 gene frequency of at least	Author's conclusion: "Our study demonstrates that the genetic risk factor

ced cutaneous adverse reaction: a meta-analysis. Pharmacogenomics 2018;19:547-52. PMID: 29629814. **ref. 4, continuation**	B*1502: D	1% were included. One study was in Han Chinese and Thai and the others in Han Chinese. The meta-analysis with oxcarbazepine-tolerant controls was based on a total of 29 cases with severe cutaneous adverse events (23 with SJS/TEN and 6 with DRESS) and 125 controls. The meta-analysis with population controls was based on a total of 30 cases with severe cutaneous adverse events (24 with SJS/TEN and 6 with DRESS) and 250 controls. Three of the four studies in the meta-analysis were included in this risk analysis separately (Chen 2017, Sun 2014, and Hung 2010). Two of the studies in this meta-analysis were included in the meta-analysis of Tangamornsuksan 2018 (Chen 2017 and Sun 2014). A meta-analysis of the data in the study of Chen 2017 was performed in Chen 2017. A random-effect model was used for the analyses, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent, but the method of data extraction was not described. Quality of the included studies was not judged. Publication bias was not analysed for the studies with severe cutaneous adverse events, only for the studies with mild and/or severe cutaneous adverse combined. Because severe cutaneous adverse events are associated and mild cutaneous adverse events are not associated with HLA-B*1502, this combined analysis provides no information. Results: Association between HLA-B*1502 and severe cutaneous adverse events (SJS or DRESS) (cases compared to oxcarbazepine-tolerant controls (carrier frequency 8.0%)): OR = 18.1 (95% CI: 6.8-48.6) (S) 62% of the cases was carrier of HLA-B*1502. Results were similar for the comparison with the population controls: OR = 14.9; 95% CI: 6.1-36.4 (S) (67% of the cases and 9.6% of the controls was carrier of HLA-B*1502). There was no heterogeneity between the studies. Note: For oxcarbazepine-induced mild cutaneous adverse events, no association with HLA-B*1502 was found in a meta-analysis of 6 studies with tolerant controls and a meta-analysis of 5 studies with population controls.	HLA-B*15:02 may be a factor in oxcarbazepine-induced severe cutaneous adverse reactions.”
ref. 5 Kim H et al. HLA-A*31:01 and oxcarbazepine-induced DRESS in a patient with seizures and complete DCX deletion. Pediatrics 2018;141:S434-S438. PMID: 29610167.	2 A*3101: D	An 11 year old girl of Turkish decent developed DRESS several weeks after start of oxcarbazepine 300 mg twice daily. She was HLA-A*3101-positive, and HLA-B*1502-, HLA-B*5701-, and HLA-B*5801-negative. The patient tested negative for infection with aerobic and anaerobic pathogens. Viral screens were also negative, with the exception of an increased Epstein-Barr virus capsid IgG antibody level of 373 U/mL and human herpesvirus 6 IgG antibody index value of 9.73. Serum concentration of oxcarbazepine was in the lower quarter of the therapeutic range. After discontinuation of oxcarbazepine and providing supportive care, the patient’s rash gradually improved, and her aspartate aminotransferase, alanine transaminase, and eosinophilia normalized over the next few days. She was discharged from hospital 9 days after admittance. According to the Naranjo causality score, the probability that the DRESS was caused by the oxcarbazepine was rated as “probable.”	Author’s conclusion: ”There is no reference to HLA-A*31:01 in the oxcarbazepine drug label, as this drug-gene association has not previously been reported. Further investigation into this association is required.”
ref. 6 Tangamornsuksan W et al. Association between	3	Meta-analysis of 2 case-control studies with oxcarbazepine-tolerant and population controls. Both included studies scored 6 out of the maximum of 9 points on the Newcastle-Ottawa scale for study quality. The meta-analysis with	Author’s conclusion: ”Strong associations between the

HLA genotypes and oxcarbazepine-induced cutaneous adverse drug reactions: a systematic review and meta-analysis. J Pharm Pharm Sci 2018;21:1-18. PubMed PMID: 29370880. **ref. 6, continuation**	B*1502: D	oxcarbazepine-tolerant controls was based on a total of 19 SJS/TEN cases and 109 controls. The meta-analysis with population controls was based on a total of 5 SJS/TEN cases and 137 controls. Both studies were in South East Asians. Both studies in this meta-analysis were included in this risk analysis separately (Chen 2017 and Sun 2014). A meta-analysis of the data in the study of Chen 2017 was performed in Chen 2017. A random-effect model was used for the analyses, but prospective registration of the protocol was not mentioned. The search and selection strategy was transparent and data extraction was standardized. Publication bias was not analysed. Results: Association between HLA-B*1502 and SJS/TEN (cases compared to oxcarbazepine-tolerant controls (carrier frequency 7.3%)): OR = 26.4; 95% CI: 7.98-87.6 (S) 68% of the cases was carrier of HLA-B*1502. Results were similar for the comparison with the population controls: OR = 30.2; 95% CI: 3.45-264 (S) (80% of the cases and 10% of the controls was carrier of HLA-B*1502) There was no heterogeneity between the studies. Note: For oxcarbazepine-induced maculopapular rash, only meta-analyses comparing cases with population controls found an association for HLA-A*3101 and HLA-B*1502. There was no association in meta-analyses comparing cases with oxcarbazepine-tolerant controls. One study found an association with HLA-B*4002 and with HLA-DRB1*0403 for both the comparisons with oxcarbazepine-tolerant and population controls.	HLA-B*1502 and oxcarbazepine-cADRs (SJS and maculopapular rash) were found in both controls from general population and oxcarbazepine-tolerant groups. There was also an association between HLA-B*3101 and oxcarbazepine-induced maculopapular rash. For patient safety, genetic screening especially for HLA-B*1502 prior to oxcarbazepine therapy at least in these closely related ethnicities is warranted.”
ref. 7 Chen CB et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology 2017;88:78-86. PubMed PMID: 27913699.	3	In a case-control study, 17 Taiwanese Han Chinese cases with oxcarbazepine-induced SJS/TEN and 6 Taiwanese Han Chinese cases with oxcarbazepine-induced DRESS were compared to 101 oxcarbazepine-tolerant controls and 3 Thai oxcarbazepine-induced SJS/TEN cases were compared to a Thai population control from a database (n = 99). A meta-analysis was performed to integrate the Han Chinese and Thai SJS/TEN data. All SJS/TEN cases had SJS with skin detachment < 5% of the total body surface area (< 1% in 85% of the cases). None of the cases died. Most cases had a good prognosis and clinical outcome during the follow-up period. Only one case had chronic ocular mucosal involvement with dry eyes and blurred vision. Oxcarbazepine-tolerant controls were defined as patients without adverse events after using oxcarbazepine for at least 3 months. The study also evaluated the safety and tolerability of alternative drugs for patients with oxcarbazepine-induced severe cutaneous adverse events. Relevant co-medication was not fully excluded, but only patients with probable or definite cause of oxcarbazepine (ALDEN score ≥4 or Naranjo algorithm ≥5) were recruited. Bonferroni correction was for the number of alleles observed in the cases (6 for SJS in Han Chinese). Prospective registration of the protocol was not mentioned and it was not specified whether the meta-analyses was planned to be performed with a random-effect or fixed-effect model. So, it is not clear whether the statistical method was chosen in advance. Studies were not included by literature search, but data collection for the cases was standardized.	Author’s conclusion: ”Our findings suggest that HLA-B*15:02 is significantly associated with oxcarbazepine-SJS in Asian populations (Chinese and Thai). However, the severity and incidence of oxcarbazepine-SJS/TEN are less than that of carbamazepine-SJS/TEN. The need for preemptive HLA-B*15:02 screening should be evaluated further.”

ref. 7, continuation

B*1502: D

A*3101: AA

Quality of the included studies was not judged with an accepted scale for study quality.
Because no published studies were included in the meta-analysis, publication bias was absent.

Results:

Association between HLA alleles and SJS:

HLA allele	ethnicity	OR	95% CI	carrier frequency in the controls
B*1502	Chinese	27.9 (S)	7.84-99.2	7.9%
		71% of the cases was carrier of HLA-B*1502		
		The positive and negative predictive values of HLA-B*1502 were calculated, based on the observed incidence of oxcarbazepine-induced SJS/TEN in Taiwan of 8.26/10,000 new users, to be respectively 0.73% and 99.97%.		
	Thai	49.0 (S)	2.39-1006	12%
		100% of the cases was carrier of HLA-B*1502		
	Chinese and Thai (meta-analysis)	30.4 (S)	9.42-97.8	10%
		75% of the cases was carrier of HLA-B*1502		
		There was no heterogeneity between the two studies.		
A*3101	Chinese	NS		3.0%
	Thai	NS		3.0%

Association between HLA alleles and DRESS (cases compared to oxcarbazepine-tolerant controls):

HLA allele	OR (95% CI)	carrier frequency in the controls
B*1502	NS	7.9%
A*3101	NS	3.0%

Safety and tolerability of alternative drugs in patients with severe cutaneous adverse events:

patients with oxcarbazepine-induced SJS	Of 2 patients receiving lamotrigine: - 1 developed DRESS (lamotrigine started 6 months after the episode of oxcarbazepine-induced SJS) - 1 was tolerant
	The only patient receiving phenytoin was tolerant.
	All patients were tolerant to all non-aromatic alternative drugs given (most commonly after the episode of oxcarbazepine-induced SJS): - clonazepam (n = 4) - levetiracetam (n = 3) - gabapentin (n = 3)

<table>
<tr><td>ref. 7, continuation</td><td></td><td>
<table>
<tr><td></td><td>- topiramate (n = 2)
- valproic acid (n = 1)
- other (methocarbamol, mephenoxalone, fludiazepam, alprazolam, diazepam, lorazepam, dabigatran, imipramine, duloxetine or zonisamide) (n = 11)</td></tr>
<tr><td>patients with oxcarbazepine-induced DRESS</td><td>All patients were tolerant to all alternative drugs given:
- lamotrigine (n = 1)
- a nonaromatic alternative drug (n = 1)</td></tr>
<tr><td rowspan="2">HLA-B*1502-positive patients with a history of carbamazepine-induced SJS/TEN</td><td>All 3 patients in the case-control study developed oxcarbazepine-induced SJS. All of these patients had an earlier onset but less clinical severity without obvious blisters or skin detachment on their trunk or extremities or systemic complications.</td></tr>
<tr><td>The authors also found 3 patients that were tolerant to oxcarbazepine.</td></tr>
</table>

Note: Both the incidence and severity of oxcarbazepine-induced SJS/TEN were lower than those of carbamazepine-induced SJS/TEN in Taiwan. The incidence of oxcarbazepine-induced SJS/TEN was 8.26/10,000 new users and the incidence of carbamazepine-induced SJS/TEN 39.0/10,000 new users (RR = 0.212; 95% CI: 0.077-0.584) (S). The calculation was based on 4,842 new users of oxcarbazepine and 14,617 new users of carbamazepine. There were no cases of mortality in the oxcarbazepine-SJS/TEN group compared to 6.5 per 100,000 new users in the carbamazepine-SJS/TEN group (RR = 0.060; 95% CI: 0.004-0.963) (S).

Note: The same authors calculated the positive predictive value of HLA-B*1502 for the development of carbamazepine-induced SJS/TEN to be 7.7% (Hung SI et al. HLA-B genotyping to detect carbamazepine-induced Stevens-Johnson syndrome: implications for personalizing medicine. Personalized Med 2005;2:225–37).</td><td></td></tr>
<tr><td>ref. 8
Sun D et al.
Association of HLA-B*1502 and *1511 allele with antiepileptic drug-induced Stevens-Johnson syndrome in central China.
J Huazhong Univ Sci Technolog Med Sci 2014;34:146-50.
PubMed PMID: 24496695.</td><td>2

B*1502: D</td><td>An 8 year old Chinese boy developed SJS 14 days after starting oxcarbazepine 450 mg/day. He was HLA-B*1502-positive. He used valproic acid and topiramate concomitantly.
The HLA-B*1502 carrier frequency was 7.9% in 38 healthy Han Chinese children from the general population and 6.3% in 32 aromatic antiepileptic drug tolerant controls (including 8 oxcarbazepine-tolerant controls). Aromatic antiepileptic drug tolerant controls were defined as patients without cutaneous adverse events after using the aromatic antiepileptic drug for at least 2 months.</td><td>Author’s conclusion:
”It was suggested that the association between the carbamazepine-induced SJS and HLA-B*1502 allele in Han Chinese children can extend to other aromatic AEDs including oxcarbazepine and phenobarbital related SJS.”</td></tr>
<tr><td>ref. 9
Amstutz U et al.
HLA-A*31:01 and HLA-B*15:02 as genetic markers for carbamazepine hypersensitivity in</td><td>2

B*1502: AA
A*3101: AA</td><td>2 Canadian children of non-Asian ancestry with oxcarbazepine-induced SJS were identified. None of the cases had HLA-A*3101 or HLA-B*1502. Presence or absence of co-medication was not reported, but alternative causes for SJS were excluded.
In 133 carbamazepine-treated Canadian children (42 with carbamazepine-induced cutaneous adverse events and 91</td><td></td></tr>
</table>

children. Clin Pharmacol Ther 2013;94:142-9. PubMed PMID: 23588310. **ref. 9, continuation**		controls), the carrier frequency of HLA-A*3101 was 15% and of HLA-B*1502 3%. The carrier frequency of HLA-B*1502 in the carbamazepine-treated children of non-Asian descent was 0%. Note: One of the cases was positive for a proxy marker of HLA-A*3101 used by the Custom Taqman SNP Genotyping Assay of Applied Biosystems to identify HLA-A*3101. This marker is in complete linkage disequilibrium with HLA-A*3101 in a European population, but apparently not in a Canadian population including different ethnic backgrounds.	
ref. 10 Wal P et al. Genetic predisposition to oxcarbazepine induced Stevens-Johnson syndrome. Indian J Crit Care Med 2011;15:173-5. PubMed PMID: 22013310.	2 B*1518: D B*4001: D	A 38 year old Indian women with a history of drug allergy developed SJS in the period of 10-14 days after starting oxcarbazepine (600 mg/day during the first 3 days and 900 mg/day thereafter). She was carrier of HLA-B*1518 and HLA-B*4001. She did not use other drugs concomitantly. After systemic corticosteroid and antihistamine treatment for 10 days, the patient improved and was discharged from the hospital.	
ref. 11 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.	3 B*1502: D	In a case-control study, 3 Taiwanese Han Chinese cases with oxcarbazepine-induced SJS were compared to 93 healthy subjects randomly selected from a biobank under a nationwide Taiwanese population study. 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: Association between HLA-B*1502 and SJS (cases compared to population controls (carrier frequency 7.5%)): OR = 80.7; 95% CI: 3.8-1714 (S) 100% of the cases was carrier of HLA-B*1502. Note: The 3 cases were identified in the same hospitals and by the same authors as the cases in Chen 2017. However, the inclusion period was earlier although partly overlapping (2002-2008 versus 2006-2014) and Chen 2017 does not refer to Hung 2010, suggesting no overlap between these 3 cases and the 17 cases in Chen 2017.	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."
ref. 12 Shankarkumar U et al. HLA B*1502 allele association with oxcarbamazepine-induced skin reactions in epilepsy patient from India. Epilepsia 2009;50:1837-8. PubMed PMID: 20831525.	1 B*1502: D	A 9 year old Indian boy developed high fever (39.4°C) with rigors, severe itching over his whole body, erythematous rash over face and hands, and a toxic appearance within hours after taking 150 mg oxcarbazepine. Oxcarbazepine was discontinued. Three months later, he developed a similar reaction 1 hour after taking another dose of oxcarbazepine 150 mg. In both cases, he responded well to antipyretics and antihistamines. A final diagnose of skin allergy as an early manifestation of SJS due to oxcarbazepine was made. No concomitant medication was reported. The patient was HLA-B*1502-positive. Note: Some characteristics of this case are atypical of SJS and thus question the diagnosis made. SJS is a delayed hypersensitivity reaction and not an almost immediate reaction. In addition, typical SJS symptoms like blistering, mucosal involvement or skin detachment were not reported.	
ref. 13 Lin LC et al.	2	A 9 year old Taiwanese boy developed SJS in the period of 14-16 days after starting oxcarbazepine (300 mg/day (7.5	Author's conclusion:

Oxcarbazepine-induced Stevens-Johnson syndrome: a case report. Kaohsiung J Med Sci 2009;25:82-6. PubMed PMID: 19321411. **ref. 13, continuation**	B*1518: D B*4001: D	mg/kg per day) during the first week and 600 mg/day (15 mg/kg per day) thereafter). He was carrier of HLA-B*1518 and HLA-B*4001. He did not use other drugs concomitantly. After systemic steroid and antihistamine treatment for 7 days, the patient improved and he was discharged from the hospital in a good general condition 12 days later. Note: The patient was tolerant to phenytoin when he was 6 months old.	"The genetic significance of HLA-B*1518 in association with oxcarbazepine-induced SJS needs to be further studied."
ref. 14 SmPC Trileptal (oxcarbazepine) 25-03-21.	0 HLA-B*1502: AA	<u>Warning</u>: Dermatological effects Serious dermatological reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (syndrome of Lyell), and erythema multiforme, have been reported very rarely in association with Trileptal use. Hospitalisation may be required for patients with serious dermatological reactions, because these reactions may be life threatening and in very rare cases fatal. Cases associated with Trileptal were observed both in children as in adults. The mean time of symptom onset was 19 days. Recurrence of the serious skin reactions following rechallenge with Trileptal has been reported in some isolated cases. Patients developing a skin reaction when using Trileptal, should be evaluated directly and Trileptal treatment should be discontinued immediately, unless the skin reaction is clearly not drug-related. In case of treatment discontinuation, substituting other antiepileptic treatment for Trileptal should be considered to avoid deprivation symptoms. Trileptal should not be started again in patients that discontinued treatment due to hypersensitivity reactions. HLA-B*1502 allele – Han Chinese, Thai and other Asian populations HLA-B*1502 is strongly associated with the risk of developing severe cutaneous skin reactions, known as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), in individuals of Han Chinese or Thai ancestry treated with carbamazepine. Because the chemical structure of oxcarbazepine is similar to that of carbamazepine, it is possible that HLA-B*1502 positive patients are also at risk for SJS/TEN during treatment with oxcarbazepine. Some data suggest this association with oxcarbazepine to exist. The prevalence of HLA-B*1502 carriers among Han Chinese and Thai is approximately 10%. If possible, these individuals should be screened for this allele before starting treatment with carbamazepine or a chemically related active substance. For HLA-B*1502 positive patients, use of oxcarbazepine can be considered if the benefits are expected to be larger than the risks. Because of the prevalence of this allele in other Asian populations (for example more than 15% in the Philippines and in Malaysia) genetic screening for the presence of HLA-B*1502 can be considered for patients from risk populations. The prevalence of the HLA-B*1502 allele is negligible in e.g. people of European ancestry, African populations, the investigated Latin-American populations and in Japanese and Koreans (<1%). Allele frequencies indicate the percentage chromosomes in the population carrying a particular allele. Because an individual carries two copies of each chromosome, but only one copy of the HLA-B*1502 allele can be sufficient to increase the risk of SJS, the percentage of patients at risk is almost twice the allele frequency. HLA-A*3101 allele – European ancestry and Japanese populations Some data indicate a possible association between HLA-	

ref. 14, continuation	HLA-A*3101: AA	A*3101 in European and Japanese populations and an increased risk of carbamazepine-induced cutaneous adverse reactions, including SJS, TEN, drug-induced skin rash with eosinophilia (DRESS) or less serious acute generalised exanthematous pustulosis (AGEP) and maculopapular skin rash. The frequency of the HLA-A*3101 allele differs strongly between ethnic populations. The HLA-A*3101 allele has a prevalence of 2-5% in European populations and a prevalence of approximately 10% in the Japanese population. In individuals of European ancestry, the presence of the HLA-A*3101 allele increases the risk of carbamazepine-induced (mostly less severe) skin reactions from 5% in the general population to 26.0%, while the absence of this the allele decreases the risk from 5% to 3.8%. HLA-A*3101 allele – other ancestries The frequency of this allele is estimated to be less than 5% in the majority of the Australian, Asian, African and North-American populations, with some exceptions of between 5 and 12%. In some ethnic groups in South-America (Argentina and Brasil), North-America (USA Navajo and Sioux and Mexico Sonora Seri) and South-India (Tamil Nadu), the frequency is estimated to be more than 15%. In other native populations in the same regions, the estimated frequency is between 10% and 15%. Allele frequencies indicate the percentage chromosomes in the population carrying a particular allele. Because an individual carries two copies of each chromosome, but only one copy of the HLA-A*3101 allele can be sufficient to increase the risk of SJS, the percentage of patients at risk is almost twice the allele frequency. There are insufficient data for a recommendation for screening of HLA-A*3101 before starting treatment with carbamazepine or chemically related substances. If a patient of European or Japanese ancestry is known to be HLA-A*3010 positive, use of carbamazepine or chemically related substances can be considered if the benefits are expected to be larger than the risks. Limitations of genetic screening Genetic screening results should never replace appropriate clinical vigilance and patient treatment. Many HLA-B*1502 positive Asian patients treated with Trileptal will not develop SJS/TEN. HLA-B*1502 negative patients of each ethnicity can still develop SJS/TEN. The same is true for HLA-A*3101 and the risk of developing SJS, TEN, DRESS, AGEP or maculopapular rash. The development of these severe cutaneous adverse reactions and the related morbidity caused by other possible factors, such as AED dose, therapy compliance, concomitantly used drugs, co-morbidities and the degree of dermatological surveillance have not been investigated. Information for health care professionals In case of screening for the presence of the HLA-B*1502 allele, high-resolution “HLA-B*1502 genotyping” is recommended. The test is positive if one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. In case of screening for the presence of the HLA-A*3101 allele, high-resolution “HLA-A*3101 genotyping” is also recommended. The test is positive if one or two HLA-A*3101 alleles are detected and negative if no HLA-A*3101 alleles are detected. <u>Adverse events</u>: Rare: drug-induced rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP). Very rare: Stevens-Johnson syndrome, toxic epidermal	

ref. 14, continuation		necrolysis (Lyell syndrome).	
ref. 15 SmPC Oxtellar XR (oxcarbazepine), USA, 13-12-18.	0 HLA-B*1502: AA	Warning: Serious dermatological reactions Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in both children and adults treated with immediate-release oxcarbazepine use. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following rechallenge with immediate-release oxcarbazepine has also been reported. The reporting rate of TEN and SJS associated with immediate-release oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million person years. Therefore, if a patient develops a skin reaction while taking Oxtellar XR®, consider discontinuing Oxtellar XR® use and prescribing another AED. Association with HLA-B*1502 Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with Oxtellar XR® treatment. Human Leukocyte Antigen (HLA) allele B*1502 increases the risk for developing SJS/TEN in patients treated with carbamazepine. The chemical structures of immediate release oxcarbazepine and Oxtellar XR are similar to that of carbamazepine. Available clinical evidence, and data from nonclinical studies showing a direct interaction between immediate release oxcarbazepine and HLA-B*1502 protein, suggest that the HLA-B*1502 allele may also increase the risk for SJS/TEN with Oxtellar XR®. The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations, is about 8% in Thai populations, and above 15% in the Philippines and in some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in people from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations, and in Japanese (<1%). Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Oxtellar XR®. The use of Oxtellar XR® should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low, or in current Oxtellar XR users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status. The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dosage, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been well characterized.	

Risk group	-

Comments:

- We only included studies with at least 1 case of a severe cutaneous adverse events in the risk analysis. If cases were described in different publications, only the most recent and largest publication was included. Other articles did not contribute enough to the evidence to be included.
- Existing guideline:
  Phillips EJ et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin Pharmacol Ther 2018;103:574-581. PubMed PMID: 29392710.
  CPIC indicates that HLA-B*1502 is strongly associated with greater risk of SJS and TEN in patients treated with oxcarbazepine. As references they mention Chen 2017, Sun 2014, Amstutz 2013 and Hung 2010, which are also included in our risk analysis. In addition, they mention the case report of Chen 2009 (Chen YC et al. Oxcarbazepine-induced Stevens-Johnson syndrome in a patient with HLA-B*1502 genotype. J Eur Acad Dermatol Venereol 2009;23:702-3. PubMed PMID: 18785891), which was not included in our risk analysis, because the SJS case described in this report was also included in Hung 2010. CPIC included Shankarkumar 2009 as a DRESS case report.
  CPIC indicates that evidence suggesting an association between the presence of HLA-A*3101 and oxcarbazepine-induced MPE, DRESS or SJS/TEN does not exist. As references they mention Chen 2017 and Amstutz 2013, which are both also included in our risk analysis.
  CPIC indicates that, if a patient is oxcarbazepine-naïve and HLA-B*1502 positive, oxcarbazepine should be avoided due to the greater risk of SJS/TEN. CPIC classifies this recommendation as strong. In addition, CPIC indicates that aromatic anticonvulsants other than carbamazepine and oxcarbazepine, including eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital, have very limited evidence, if any, linking SJS/TEN with the HLA-B*1502 allele, but that caution should still be used when choosing an alternative agent. They do not classify this recommendation. Finally, CPIC indicates that with regular dosing, oxcarbazepine-induced SJS/TEN usually develops within the first 4–28 days of therapy. Therefore, patients who have been continuously taking oxcarbazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk (but not zero) of oxcarbazepine-induced adverse events in the future, regardless of HLA-B*1502 status. CPIC recommends to cautiously consider use of oxcarbazepine in the future in these patients. CPIC classifies this recommendation as optional.
  CPIC mentions that data describing the relationship between HLA-B*1502 genotype and oxcarbazepine-induced cutaneous adverse reactions in paediatric patients are scarce. In the absence of data suggesting a different relationship between this HLA allele and drug-induced hypersensitivity in paediatric patients, CPIC indicates that the recommendations may be used to guide use of oxcarbazepine in both adult and paediatric patients.
  CPIC mentions potential benefits and risks of HLA-B*1502 testing. A potential benefit of HLA-B*1502 testing is a reduction in the incidence of serious, and sometimes fatal, cutaneous adverse reactions to oxcarbazepine by identifying those who are at significant risk and using alternative therapy. A potential risk of HLA-B*1502 testing is ruling out the use of oxcarbazepine in patients who may not ever develop a hypersensitivity reaction to the drug. This risk is mitigated by the fact that there are often alternatives to oxcarbazepine with comparable effectiveness; however, consideration must be given to the risk of cutaneous adverse reactions with anticonvulsants other than oxcarbazepine and carbamazepine. For example, it has been demonstrated in an Asian population that an HLA-B*1502 screening policy for carbamazepine will not decrease the overall rate of SJS/TEN if other anticonvulsants associated with SJS/TEN (e.g., phenytoin) are used instead of carbamazepine. Furthermore, other anticonvulsants may be associated with more unfavourable adverse effect profiles compared to carbamazepine or oxcarbazepine. Although genotyping is considered reliable when performed in qualified clinical laboratories, laboratory error and sample mix-up is always a distinct possibility. Genotype results are associated with a patient for a lifetime; as such, a genotyping error could have a broader impact on healthcare should other HLA-B*1502 associations be identified in the future.
  CPIC provides the following recommendations for HLA-B*1502-positive patients:
  - If patient is oxcarbazepine-naive, do not use oxcarbazepine. Other aromatic anticonvulsants[a] have weaker evidence linking SJS/TEN with the HLA-B*1502 allele; however, caution should still be used in choosing an alternative agent.
  - The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (~4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used oxcarbazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine in the future. Previous tolerance of oxcarbazepine is not indicative of tolerance to other aromatic anticonvulsants.[a]

  [a] Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.
  On 31-3-2018, there was not a more recent version of the recommendations present on the PharmGKB- and on the CPIC-site.

Date of the literature search: 18 March 2022.

	Genotype	Code	Gene-drug interaction	Action	Date
Pharmacogenetics Working group decision	HLA-B*1502	3 D	yes	yes	23 May 2022

Mechanism:
Although the mechanism of hypersensitivity for oxcarbazepine 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). Oxcarbazepine 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+	5+
Corresponding Clinical Implication Score:		Beneficial