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Pregabalin
Toxic Epidermal Necrolysis

The use of pregabalin has been associated with rare and sometimes fatal cases of Toxic Epidermal Necrolysis.

Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) share a common biological mechanism and can be viewed as a continuum in which TEN lies at the extreme of seriousness and lethality.
Pregabalin is a gamma-aminobutyric acid (GABA) analogue that binds to an auxiliary voltage-dependant calcium channel subunit in the central nervous system. It was authorized for the first time in the European Union in 2004 and is currently marketed under a great number of trademark names. Pregabalin is indicated in adult patients for the treatment of central and peripheral neuropathic pain, of epilepsy (as adjuvant therapy for partial crises with or without secondary generalization), as well as of generalized anxiety disorder.

SJS was listed in 2007 in the SmPC of the original medicinal product containing pregabalin. Since then cases of severe cutaneous adverse reactions **(SCARs)** have been reported, such as TEN, including life-threatening and fatal instances. TEN is a true medical emergency; the suspected medicine, when applicable, should therefore be promptly discontinued and treatment started. An early diagnosis is essential for prognosis.
During a Europe-wide assessment of a safety signal that was finalized in January 2022, a review was undertaken of all available data from pre-clinical and clinical studies, from the literature and from the European adverse drug reaction database EudraVigilance. A cumulative analysis was additionally performed of post-marketing cases of TEN, SJS/TEN and similar reactions. Given the pathophysiological mechanism and the clinical characteristics of TEN, a SCAR that is more serious than the already previously listed SJS, it was concluded that the information of pregabalin-containing medicinal products needed to be updated. The European Medicines Agency has decided that the **SmPC** texts should be altered to include the following:

4.4. Special warnings and precautions for use
Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

4.8. Undesirable effects
[…] rare: Toxic Epidermal Necrolysis

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In the **Information Leaflet** addressing patients, red flag signs and symptoms are explained as follows in the "Possible side effects" Section:

> [[…] serious skin reaction characterized by reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis) […] If you experience swollen face or tongue or if your skin turns red and starts to blister or peel, you should seek immediate medical advice.

Adriana Gamboa

	Interval between start of exposure to the drug and start of the reaction	General signs and symptoms	Cutaneous features	Laboratory features	Main organs affected	Histopathological features
SJS and TEN	**4 to 28 days**	Fever ≥38ºC, flu-like syndrome, respiratory symptoms	Blisters, extensive skin exfoliation (SJS <10%, TEN ≥30%, SJS-TEN 10-30%), confluent rash, atypical target lesions, purpura, Nikolsky's sign (skin slips away when rubbed)	Lymphopenia, transient neutropenia, renal impairment	Ears, nose and throat, lungs, GI tract, liver, kidneys	Whole epidermal thickness necrosis, focal necrosis of keratinocytes and skin appendages, moderate dermal infiltration with mononuclear cells, negative direct immunofluorescence test

Adapted from: Duong TA et al. Severe cutaneous adverse reactions to drugs. Lancet 2017; 390: 1996–201.

Revisit here essential SCAR features

ADRs in the Literature
Prevention of delayed hypersensitivity reactions and HLA

Type B idiosyncratic, immunologically mediated adverse reactions include **delayed hypersensitivity reactions (DHRs),** which occur six or more hours after exposure and are related to activation of cytotoxic T cells against self tissues, usually the skin but also in other organs such as the liver, lungs, kidneys or heart.
Cutaneous DHRs present in various forms but more frequently as maculopapular rashes. However, highly serious and even lethal phenotypes can also manifest themselves, such as **DRESS** (drug rash with eosinophilia and systemic symptoms) or the SJS/TEN spectrum (Stevens-Johnson syndrome / toxic epidermal necrolysis).
The human leucocyte antigen complex (**HLA complex**) has a central role in tolerance to self antigens through their presentation to T cells. Conversely, the HLA complex is also involved in the presentation of foreign antigens so that they can be cytotoxically destroyed. In any case, one of the prerequisites for T cell activation is the so-called signal 1, a highly specific interaction between HLA, antigen and T cell by means of specific receptors of the latter.
Risk HLA alleles for various DHRs have been described since 2002. In the case of **abacavir hypersensitivity syndrome,** which usually presents in the first few weeks of exposure to this HIV antiretroviral drug, with nausea, diarrhoea and sometimes rash, it has been demonstrated that allele HLA-B*57:01 has a negative predictive value (NPV) of 100% (though with a positive predictive value of only 55%). Such a high NPV has allowed for high levels of confidence when prescribing abacavir to individuals lacking the risk allele, and the occurrence of hypersensitivity syndrome has been all but virtually eliminated.
Meanwhile, for the vast majority of drugs that can cause delayed hypersensitivity, **HLA associations have low predictive values**. Moreover, an HLA association that is relevant for a given population or ethnicity may not be so for others. If the predictive value of relevant risk HLA testing for more drugs and adverse reactions is to increase, many more studies need to be undertaken that will examine the myriad genetic and environmental factors at stake.
The authors of this article discuss immunological, pharmacological and genetic factors underlying HLA-associated ADRs, as well as their potential future impact in daily clinical practice.

• Deshpande P et al. Immunopharmacogenomics: Mechanisms of HLA-Associated Drug Reactions. Clin Pharmacol Ther. 2021 Sep;110(3):607-615. doi: 10.1002/cpt.2343.

Excipients: safety information in patient leaflets – part 4

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Ethanol	Cutaneous	*This medicine contains x mg alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>> (y% w/<w><v>).* *It may cause burning sensation on damaged skin.*	• In neonates (pre-term and term newborn infants), high concentrations of ethanol (especially in a topical medicinal product applied under occlusion) may cause severe local reactions and systemic toxicity due to significant absorption through immature skin. • Depending on the product and concentration of ethanol, the warning "flammable" may be necessary. Inclusion of warnings on use near an open flame, lit cigarette or some devices (e.g. hairdryers) should be considered.
	Oral, parentheral, inhalation	***For all:*** *This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y%w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to less than A ml beer or B ml wine.* ***For medicines with a zero limit for ethanol content:*** *The small amount of alcohol in this medicine will not have any noticeable effects.* ***For medicines with a limit of either 15 or 75 mg/Kg of ethanol per dose:*** *The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.* *If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine.* *If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.* ***For medicines with a limit of 15 mg/Kg of ethanol per dose:*** *The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy.* ***For medicines with a limit of 75 mg/Kg of ethanol per dose:*** *The alcohol in this preparation is likely to affect children. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities.* *The amount of alcohol in this medicine can affect your ability to drive or use machines. This is because it may affect your judgement and how fast you react.* *If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine.*	• Para calcular o volume equivalente de cerveja e vinho, assume-se um conteúdo em etanol na cerveja de 5% v/v (álcool por volume), que é equivalente a 4% m/v, e um conteúdo em etanol no vinho de 12,5 % v/v ou 10% m/v (a gravidade específica do etanol é cerca de 0,8). • Os volumes de cerveja e vinho (A e B) são arredondados para o número inteiro seguinte. • Quando o etanol está presente como um componente do processo de fabrico (por exemplo no revestimento de comprimidos) ou como solvente de extração e é evaporado, não é necessário mencioná-lo. • Quando uma dose é dada durante um período prolongado (ex.: por perfusão lenta durante várias horas), o aumento da concentração de álcool no sangue será inferior e os seus efeitos podem ser reduzidos. Nestes casos, o Folheto Informativo e o Resumo das Características do Medicamento devem incluir uma frase, como por ex.: Como este medicamento é habitualmente dado de forma lenta durante XX horas, os efeitos do álcool podem ser reduzidos.

Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Ambrisentan *Volibris*	**Patients**	**Reminder Card** 28-01-2022
Dostarlimab *Jemperl*	**Patients**	**Card** 13-01-2022
Lenalidomide *Lenalidomida Accord* *Lenalidomida Fresenius Kabi* *Lenalidomida Generis* *Lenalidomida Krka* *Lenalidomida Mylan* *Lenalidomida Pharmakern* *Lenalidomida Sandoz* *Lenalidomida Stava* *Lenalidomida Teva* *Lenalidomida Zentiva*	**Physicians:** haematology **Pharmacists:** hospital pharmaceutical service directors at hospitals with the specialty of haematology	**Safety information** **Advice lists for patients who are:** **Males** **Females of childbearing potential** **Females without childbearing potential** **Reporting forms for:** **Pregnancy** **Adverse event**
	Patients	**Booklets for patients who are:** **Males** **Females of childbearing potential** **Females without childbearing potential** 31-01-2022
Mecasermin *Increlex*	**Physicians:** specialists in paediatric endocrinology and paediatricians who conduct paediatric endocrinology clinics in hospitals	**Safety information** 31-01-2022
Micafungin *Micafungina Reig Jofre*	**Physicians:** infectious diseases specialists, and intensive care, infectious diseases, internal medicine, general surgery, microbiology, transplant unit and paediatrics department directors	**Prescribing checklist** 12-01-2022
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To be continued ►

Cont´d ▶

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INN Medicinal product	Target	Materials? Online publication date
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Trastuzumab emtansine *Kadcyla*	**Physicians:** oncologists, radiotherapists, general surgeons, gynaecologists and internists, in charge of senology and experienced in the use of anti-HER2 therapies **Nurses:** hospital **Pharmacists:** hospital	Healthcare professionals guide 04-01-2022

Compiled by Patrícia Catalão