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Severe Cutaneous Adverse Reactions (SCAR) to Drugs
– a reference* for healthcare professionals

Severe cutaneous adverse reactions (**SCAR**) to drugs include Stevens-Johnson syndrome (**SJS**), toxic epidermal necrolysis (**TEN**), drug-reaction with eosinophilia and systemic symptoms (**DRESS**) as well as, on account of rash extension and systemic symptoms, acute generalized exanthematous pustulosis (**AGEP**).

The **incidence** of these reactions is low. It is estimated at two cases per million people for SJS and TEN, and at 1 out of every 1,000 to 10,000 new users of antiepileptic drugs for DRESS. Though rare, these reactions can be fatal or cause serious sequelae – an **early diagnosis is crucial** so that the offending drug can be immediately discontinued and appropriate treatment started.

SCARs are considered to be **non-immediate hypersensitivity reactions**. Their heterogeneity may be explained by activation of varying types of effector or regulator cells secreting specific cytokines. The following adapted **table** highlights their main clinical and histopathological features.

	Time between start of exposure to drug and start of reaction	General signs and symptoms	Cutaneous features	Laboratory	Major affected organs	Histopathology
SJS and TEN	**4-28 days**	Fever ≥38ºC, flu-like syndrome, respiratory tract symptoms	Blisters, extensive sloughing (SJS <10%, TEN ≥30%, SJS-TEN 10-30%), confluent erythema, atypical target lesions, purpura, Nikolsky's sign (skin detachment with sliding finger pressure)	Lymphopenia, transient neutropenia, renal impairment	Ears, nose and throat, lungs, GI tract, liver, kidneys	Necrosis in whole thickness of epidermis, focal necrosis of skin appendages and keratinocytes, moderate dermal mononuclear cell infiltrate, negative direct immunofluorescence test
DRESS	**2-6 weeks**	Fever ≥38ºC, flu-like syndrome	Maculopapular rash, erythroderma, oedema of the face or extremities, purpura, focal and monopolar mucosal involvement	Eosinophilia >700 cells/µL, atypical lymphocytes, raised transaminases, renal impairment, herpesvirus (HHV-6, HHV-7, EBV, CMV) reactivation, parvovirus B19 reactivation	Liver, kydneys, lungs, muscle, heart, pancreas, bone marrow, lymph nodes (in 2 or more sites)	Lichenoid infiltrate or eczematous pattern, focal keratinocyte necrosis, mononuclear infiltrate, focal eosinophil and neutrophil infiltrates, mild vasculitis
AGEP	**1-11 days**	Fever ≥38ºC	Intertriginous erythema, oedema, disseminated sterile non-follicular pustules, postpustular pinpoint desquamation, Nikolsky's sign, oral mucosa rarely involved	Hyperleucocytosis, neutrophils ≥7000 cells/µL, mild eosinophilia	Rare: liver, lungs	Subcorneal or intraepidermal pustules, with or without papillary oedema, focal keratinocyte necrosis, sometimes neutrophilia and eosinophilia, mild vasculitis

Cont'd ▶

INDEX CARD

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▶ *Cont'd*

SSJ and TEN are viewed as variants in a **spectrum**. Typical dermatological features are often preceded by general manifestations. Two or more mucosae are affected in 80% of cases, also frequently preceding the skin lesions. Histological confirmation of whole-thickness epidermal necrosis and a negative direct immunofluorescence test are essential, though a specific diagnostic test or algorithm is not available. It should be noted that an **offending drug is found in 30% of cases whereas in 15% causality associated with a medicine is unlikely**.

The diagnosis of **DRESS** is difficult given the complexity of the natural evolution of this clinically heterogeneous syndrome, including visceral symptoms with or without skin involvement. The **prodromal stage** can precede the skin rash by two weeks, presenting with fever, lymphadenopathy, flu-like syndrome, pain or burning sensation, or pruritus. DRESS can cause reactivation of one or multiple members of the human herpesvirus family. Long-term relapses have also been described.

Should a diagnosis of SJS, TEN or DRESS be confirmed, the condition should be treated and followed up in a specialized unit. **A diagnosis of SJS or TEN in the first seven days** is associated with greater survival comparatively to a more delayed diagnosis.

AGEP is considered to be the least serious of the four, and is usually **transient and benign**. The first sites to be affected are the intertriginous areas (armpits, groin), the trunk and the upper extremities.

Causality assessment in a case of SCAR should take into account several factors, such as the case's specific clinical manifestations, the medicinal product's characteristics, and the time between drug administration and the appearance of symptoms. The drug exposure – start of SCAR time gap is usually short for AGEP, intermediate for SJS and TEN, and long for DRESS. **A medicine that has been suspended before the start of a SCAR can still be suspected as a cause should it have a long half-life**.

Other causality algorithms notwithstanding, the **ALgorithm for Drug causality in Epidermal Necrolysis (ALDEN)** has been validated to improve the causality assessment of individual cases of SJS and NET. It uses data on time since the medicine was first administered, on the medicine's pharmacokinetics, on suspension or reintroduction, as well as on notoriety (known high-risk medicines – see table below).

Drugs frequently associated with:		
SJS/TEN Creamer D et al. Br J Dermatol. 2016;174:1194–227	**DRESS** Cacoub P et al. Am J Med. 2011;124:588-97	**AGEP** Sidoroff A et al. Br. J.Dermatol. 2007;157:989–96.
Allopurinol Carbamazepine Lamotrigine Nevirapine Non-steroidal antiinflammatory drugs Oxicam Phenobarbital Phenytoin Sulphamethoxazole and other sulfonamides Sulfasalazine	Abacavir Allopurinol Carbamazepine Lamotrigine Nevirapine Phenobarbital Phenytoin Sulfasalazine	Diltiazem Hydroxychloroquine Penicillins Quinolones Sulfonamides Terbinafine

Early diagnosis and specialist treatment are essential so that long-term sequelae or fatal outcomes of SCAR can be prevented or limited. Physicians and other healthcare professionals need therefore stay up to to date and clinically aware for any potential causal associations between this type adverse reactions and unexpected medicinal products.

Ana Severiano

**** Duong TA et al. Severe cutaneous adverse reactions to drugs. Lancet 2017; 390: 1996–2011***

Educational Materials published in the Infomed product information webpage
Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Abacavir **Abacavir + Lamivudine** Abacavir Mylan Abacavir + Lamivudina Mylan	**Physicians:** with experience in HIV therapy, hospital infectious diseases and internal medicine department directors. **Pharmacists**: hospital pharmacy service directors.	Hypersensitivity reactions 30/10/2018
Adalimumab Amgevita	**Physicians:** hospital rheumatology, dermatology and gastroenterology department directors.	Guide on main safety risks
	Patients	Patient alert card Paediatric patient alert card 12/10/2018

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Adrenaline Epipen	**Physicians:** respiratory medicine, paediatrics and allergy specialists.	Prescriber checklist
	Patients and/or caregivers	Educational brochure Educacional videoclip 26/10/2018
Alemtuzumab Lemtrada	**Physicians:** neurology.	Guide (safety risks and monitoring) Prescriber checklist
	Patients	Patient guide Alert card 02/10/2018
Atezolizumab Tecentriq	**Physicians:** pneumologists with experience in lung cancer treatment; urologists with experience in bladder cancer treatment; oncologists with experience in lung and/or bladder cancer treatment.	Safety guide
	Patients	Alert card 12/10/2018
Phentanyl PecFent	**Physicians:** oncologists, pain and palliative care specialists. **Pharmacists:** community and hospital pharmacies.	Guide (risk minimization)
	Patients and healthcare providers	Patient and healthcare provider guide 11/10/2018
Dimethyl fumarate Skilarence	**Physicians:** dermatologists.	Guide on the risk of serious infections 12/10/2018
Hydroxycarbamide Siklos	**Physicians:** haematology, oncology, endocrinology and paediatrics.	Treatment guide in sickle cell anaemia
	Patients	Patient guide – in sickle cell anaemia 31/10/2018
Methylphenidate Metilfenidato Farmoz Metilfenidato Sandoz	**Physicians:** paediatrics, neuropaediatrics and psychiatry.	Prescription guide Pre-prescription checklist Ongoing treatment monitoring checklist Ongoing treatment monitoring table 15/10/2018
Ocriplasmin Jetrea	**Patients**	Treatment guide – pdf Treatment guide – audio CD 31/10/2018
Rituximab Rixathon	**Physicians:** rheumatology and internal medicine.	Non-oncological indications
	Physicians: haematologists and oncologists. **Pharmacists:** hospital. **Nurses:** hospital.	Alert card for chronic lymphocytic leukaemia (CLL) and non-Hodgkin lymphoma (NHL)
	Patients	Non-oncological indications 30/10/2018
Magnesium sulphate + Potassium sulphate + Sodium sulphate Eziclen	**Physicians:** gastroenterology.	Leaflet on the relevance of adequate hydration
	Patients	Instructions and registry form 03/10/2018

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Communications to Healthcare Professionals published on the Infarmed website

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INN Medicinal product	Target	Comunication Online publication date
Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin and prulifloxacin Products containing fluoroquinolones for systemic and inhalatory routes	**Physicians:** general/family medicine, ENT, pneumology, urology, nephrology, infectious diseases, internal medicine, cardiology, radiology and intensive medicine.	Risk of aortic aneurysm and dissection 09/10/2018
Dexamethasone Ozurdex	**Physicians:** ophthalmologists specialized in retina, at private and state clinics and hospitals.	Inspection finding of a silicone particle in implant List of marketed batches with confirmed particle presence and which were subjected to immediate recall (communication annex) 24/10/2018
Hydrochlorothiazide (single or in combination) Products containing hydrochlorothiazide	**Physicians:** general/family medicine, internal medicine, cardiology, nephrology, geriatrics and dermatology. **Pharmacists:** community and hospital pharmacies.	Risk of non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma) 12/10/2018
Ocriplasmin Jetrea	**Physicians:** ophthalmologists. **Pharmacists:** community and hospital pharmacies. **Nurses:** in ophthalmology departments.	0.375 mg/0.3 ml injectable solution – no need for dilution before injection 18/10/2018
Rivaroxaban Xarelto	**Physicians:** intervention cardiologists in state and private hospitals where TAVI procedures are undertaken; Portuguese Association of Cardiovascular Intervention (APIC).	Increased all-cause mortality, thromboembolic and haemorrhagic events, in patients undergoing transcatheter aortic valve implantation in prematurely discontinued clinical trial 03/10/2018
Sildenafil Revatio Viagra	**Physicians:** gynaecology and obstetrics.	Sildenafil should not be used for the treatment of intrauterine growth restriction 11/10/2018
Ulipristal EllaOne	**Physicians:** gynaecology and obstetrics, general/family medicine. **Pharmacists:** community.	Pregnancy Registry 15/10/2018

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