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Warfarin
Anticoagulant-Related Nephropathy

Anticoagulant-related nephropathy seems to be underdiagnosed. It can cause irreversible kidney injury and decrease survival.

Warfarin is a classic (coumadin) anticoagulant that is often called a vitamin K antagonist because that is its baseline mechanism of action. Warfarin inhibits reduction of vitamin K to vitamin KH2, which results in inhibition of vitamin K dependent coagulation factors and of anticoagulant proteins. Warfarin is indicated for the treatment and prophylaxis of venous thrombosis and pulmonary embolism, as well as for the prophylaxis of thromboembolic phenomena in patients with atrial fibrillation and prosthetic heart valves.
Anticoagulant-related nephropathy (ARN), known earlier as warfarin-related nephropathy, is a type of acute kidney injury that can be caused by excessive anticoagulation. ARN is characterized by profuse glomerular bleeding that is reflected in histopathological terms in renal biopsies as a great number of renal tubules filled with erythrocytes and erythrocyte casts. Elderly patients with underlying chronic renal disease seem to be at higher risk. ARN is associated with decreased survival and with renal injury irreversibility, irrespective of the presence or absence of previous nephropathy.

During routine safety signal detection activities, and following a review of all available data, including from the European adverse drug reaction database (Eudravigilance) and from a literature review, a possible association between warfarin and ARN was identified. This was shown thanks to renal biopsy data and positive dechallenge and rechallenge effects (i.e., improvement following drug discontinuation and worsening of nephropathy on resumption of warfarin). In almost every case of acute renal injury, patients presented with supratherapeutic INR levels and serum creatinine elevation.
ARN is probably underdiagnosed mainly on account of the following factors: it is difficult to recognize, it is more frequent in patients with multiple risk factors for acute kidney injury of any cause, it presents with a type of lesion that is more often ascribed to other major aetiologies, and renal biopsies are contraindicated in patients who are on therapeutic anticoagulation.
In order to alert to a probable underdiagnosis of ARN and for anticoagulated patients to be further monitored, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the texts of the Summaries of the Product's Characteristics (SmPCs) of medicinal products containing warfarin be changed to include the following update:

Cont'd overleaf ▶

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▶*Cont´d*

4.4. Special warnings and precautions for use

Anticoagulant-related nephropathy

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and hematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with a supratherapeutic INR and hematuria (including microscopic).

4.8. Efeitos indesejáveis

Renal and urinary disorders

Frequency 'not known': Anticoagulant-related nephropathy (see section 4.4)

Adriana Gamboa

Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials Online publication date
Deferasirox *Deferasirox Mylan*	**Physicians:** immuno-haemotherapy specialists, haematologists and paediatricians	Guide
	Patients	Guide
		09-02-2022
Deferasirox *Deferasirox Accord* *Deferasirox Generis*	**Physicians:** immuno-haemotherapy specialists, haematologists and paediatricians	Manual
	Patients	Manual
		28-02-2022
Siponimod *Mayzent*	**Physicians:** neurologists treating multiple sclerosis	Checklist
	Patients	Guide for the patient/caregiver
		16-02-2022
Rivaroxaban *Xarelto*	**Physicians:** Physicians: paediatric cardiologists, paediatricians, paediatric oncologists, haematologists, paediatric surgeons, cardiologists, orthopaedic surgeons, family medicine / general practice physicians, vascular surgeons, internists	Guide
		09-02-2022

Compiled by Patrícia Catalão

Excipients: safety information in patient leaflets – part 5

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Phenylalanine	All	*This medicine contains x mg phenylalanine in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *Phenylalanine may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.*	• Seel also Aspartame.
Formaldehyde	Topical Oral	*May cause local skin reactions (e.g. contact dermatitis).* *May cause stomach upset and diarrhea.*	
Phosphate buffers	Ocular	*This medicine contains x mg phosphates in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *If you suffer from severe damage to the clear layer at the front of the eye (the cornea), phosphates may cause in very rare cases cloudy patches on the cornea due to calcium build-up during treatment.*	• Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.
Fructose	Oral Parentheral (non-IV)	*This medicine contains x mg fructose in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *[If the medicine is in contact with teeth (e.g. oral liquids, lozenges or chewable tablets) and is intended for long term use:] Fructose may damage teeth.* *If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.*	• Fructose effetively masks the unpleasant taste of certain tablet formulations. • The cumulative effect of the concomitant administration of fructose (or sorbitol) containing products should be taken into consideration, as well as the dietary intake of fructose (or sorbitol).
	Intravenous (IV)	*If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose in this medicine, which may cause serious side effects.* *You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.*	• Coprecipitation of fructose with hydrophobic drugs improves the dissolution profile of the latter. • Children under 2 years of age may have not yet been diagnosed with hereditary fructose intolerance (HFI). Medicines containing fructose must in general be contraindicated in this population.

Communications to Healthcare Professionals published on the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Communication Online publication date
Anagrelide *Anagrelida Accord* *Anagrelida Aurovitas* *Anagrelida Bluefish* *Anagrelida Teva* *Xagrid*	**Physicians:** haematologists, day hospitals with the specialty of haematology, internists	Risk of thrombosis including cerebral infarction after sudden discontinuation of treatment 22-02-2022
Cladribin *Mavenclad*	**Physicians:** neurologists, Portuguese Society of Neurology, Multiple Sclerosis Study Group, Portuguese Gastroenterology Society, and Portuguese Society of Paediatric Gastroenterology, Hepatology and Nutrition	Risk of serious liver injury, and new recommendations on liver function monitoring 14-02-2022
Donepezil *Aricept* *Donepezilo Alter Genéricos* *Donepezilo Aurovitas* *Donepezilo Bluepharma* *Donepezilo Ciclum* *Donepezilo Farmoz* *Donepezilo Fixime* *Donepezilo Genedec* *Donepezilo Generis* *Donepezilo Jaba* *Donepezilo KRKA* *Donepezilo Lixben* *Donepezilo Mylan* *Donepezilo Pharmakern* *Donepezilo Ratiopharm* *Donepezilo Sandoz* *Donepezilo Teva* *Donepezilo toLife* *Donepezilo Vitória* *Donepezilo Zentiva*	**Physicians:** neurologists and psychiatrists	Safety information concerning heart conduction disorders, including QT interval prolongation and torsade de pointes 01-02-2022
Irinotecan *Irinotecano Accord* *Irinotecano Aurovitas* *Irinotecano Hikma* *Irinotecano Kabi*	**Physicians:** oncologists	Patients with decreased uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) are at increased risk of serious neutropenia and diarrhoea 28-02-2022

Compiled by Patrícia Catalão