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Remdesivir for COVID-19: an overview of safety issues

Remdesivir was the first medicine for COVID-19 conditionally authorized in the EU for purposes of access facilitation in the context of the current pandemic emergency. Data were assessed within an exceptionally short timeframe and assessment is ongoing as new data arise. EMA has concluded that the benefit-risk balance is favourable in patients with pneumonia requiring supplementary oxygen, that is, seriously ill patients.

The conditional Marketing Authorization Holder is required to present additional data to EMA, including the final results of studies that are already under way.

The SPC and PIL of remdesivir features an **inverted black triangle**, which means that the product is subjected to additional monitoring for expedited detection of potential safety problems and implementation of risk prevention measures. It is therefore all the more important that healthcare professionals communicate any suspected ADRs from their clinical practice.

Remdesivir is indicated in the treatment of **COVID-19 with pneumonia requiring supplementary oxygen**. It is recommended for adults and adolescents older than 12 years and weighing at least 40 kg, and it is given by IV route.

The **adverse reactions listed** in the product's **SPC** are: raised transaminases (very common), headache (common), nausea (common), skin rash (common), hypersensitivity (rare), and infusion-related reactions (rare). The following should also be borne in mind:

- Infusion-rate related adverse reactions. **Slower infusion rates**, which can take as long as up to 120 minutes, can prevent anaphylactic-like reactions, including hypotension, bradycardia, dyspnoea, etc.
- There are no available data for recommending dosage adjustments in kidney and liver failure. Remdesivir is actually not recommended in cases of either renal or hepatic insufficiency, since elevation of transaminases was observed in clinical trials and serious renal toxicity was observed in rodents and monkeys. Kidney and liver functions should be monitored throughout treatment, which should be discontinued in case of analytical changes.

Cont'd overleaf ▶

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- On account of in vitro studies showing an antagonistic effect of **hydroxychloroquine** on **remdesivir**'s antiviral activity, **simultaneous administration** of both medicines is not recommended.

How can healthcare professionals contribute to further the knowledge on the safety profile of remdesivir?

Information acquired from following up patients is of great relevance, especially allergic, renal and hepatic adverse reactions. Any suspected ADR can be easily reported through **Portal RAM**, at Infarmed's website. You can find FAQs and tips on how best to use this tool **here**. And you can also use the following email address: farmacovigilancia@infarmed.pt .

Collaborating with the National Pharmacovigilance System to protect public health is everyone's responsibility: please report!

Fátima Pereira de Bragança

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

Communications to Healthcare Professionals published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Leuprorelin Eligard	**Physicians:** urologists and oncologists **Nurses:** hospital urology and oncology depts, and community health centre nursing teams **Pharmacists:** hospital pharmaceutical service directors	Reconstitution and administration instructions to be followed closely 06-08-2020
Talidomide Talidomida Accord	**Physicians:** haematologists and clinical directors **Pharmacists:** pharmaceutical service directors at hospitals where the product is prescribed and dispensed	Risk of teratogenicity, serious infections (sepsis, septic shock and hepatitis B virus reactivation), acute myeloid leukaemia and myelodysplastic syndromes, incidence of second primary neoplasms, and off-label use 15-08-2020

Compiled by Patrícia Catalão

ADRs in the literature
Drug-induced liver injury: types and phenotypes

Drug-induced injury is an uncommon but highly relevant form of liver pathology. Whereas the pathophysiology of direct and indirect hepatotoxicity is reasonably well known, significant gaps remain in our knowledge about idiosyncratic forms. Among prescription-only medicines, antimicrobial agents, often of rather common use, are the ones most frequently associated with idiosyncratic liver injury.

Recently an allele outside the HLA region has been identified in genomic studies, which may be associated with idiosyncratic hepatotoxicity. A hypothesis has emerged involving the coming together of various factors and a common immunological response. The latter could originally be triggered as a reaction to an abnormal drug metabolite produced by the liver and presented to the surface of hepatocytes.

The characteristics of the three major types of drug-induced hepatotoxicity are summed up below following the criteria proposed by the authors of this review published in the New England Journal of Medicine.

Idiosyncratic hepatotoxicity: rare

- not dose related, unpredictable
- latency since start of exposure: highly variable (days to years)
- examples of phenotypes: acute or chronic, cholestatic or mixed hepatitis
- examples of agents most often involved: amoxicillin clavulanate, cephalosporins, isoniazid, nitrofurantoin, minocycline, fluoroquinolones, macrolides

Indirect hepatotoxicity at liver or immunological system level: uncommon

- not dose related, partially predictable
- latency since start of exposure: relatively long (months)
- examples of phenotypes: acute hepatitis, chronic hepatitis, non-alcoholic fatty liver
- examples of agents most often involved: antineoplastic agents, glucocorticoids, monoclonal antibodies

Direct hepatotoxicity from high drug doses: common

- dose related, predictable
- latency since start of exposure: typically short (days)
- examples of phenotypes: elevation of liver enzymes, acute hepatic necrosis
- examples of agents most often involved: paracetamol, aspirin, cocaine, amiodarone IV, chemotherapeutic agents

The article goes on to discuss the growing role of **medicinal herbs and food supplements** in the proportion of cases of hepatotoxicity, which has gone up from 7-9% in 2004-2007 to 19-20% in 2010-2014, and which may reflect either increased consumption and/or less intensive regulatory oversight.

The products that are more often involved are not so much medicinal herbs or diet supplements used in isolation than multi-ingredient food supplements being promoted for weight control, muscular enhancement, improved sexual function, mental acuity or general well-being. These products often contain up to twenty different ingredients, including vitamins, minerals, proteins and plant-based products of sometimes uncertain quality and concentrations. In these cases, the most frequent phenotype is hepatocellular hepatitis with a high rate of fulminant liver failure.

- ***Hoofnagle JH, Björnsson ES. Drug-Induced Liver Injury – Types and Phenotypes. N Engl J Med. 2019 Jul 18;381(3):264-273.***

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Esketamine Spravato	**Physicians:** psychiatrists **Nurses:** heads of nursing	Guide for healthcare professionals Checklist: fitness for discharge from healthcare facilities
	Patients	Patient guide 10-08-2020
Fingolimod Gilenya	**Physicians:** neurologists, neuropaediatricians and gynaecologists/ obstetricians involved in the treatment of multiple sclerosis	Prescriber's checklist
	Patients	Patient guide Pregnancy-specific alert card 05-08-2020
Rituximab Ruxience	**Physicians:** haematologists **Nurses:** hospital **Pharmacists:** hospital	Healthcare professional guide – oncological indications
	Physicians: rheumatologists and internists	Healthcare professional guide – non-oncological indications
	Patients	Patient's guide - non-oncological indications Alert card – non-oncological indications 12-08-2020
Rivastigmine Rivastigmina Generis, adesivo transdérmico	**Patients**	Memory card and instructions for use 05-08-2020
Talidomide Talidomida Accord	**Physicians:** haematologists **Pharmacists:** pharmaceutical service directors at hospitals where the product is prescribed and dispensed	Healthcare professional guide Recording and dispensation flowchart
	Physicians: haematologists	Decision algorithm for starting treatment Checklist for starting treatment Prescription authorization form **Start of treatment forms:** – Women of childbearing potential – Women of non-childbearing potential – Males **Pregnancy exposure forms:** – History and early pregnancy – Pregnancy outcome Adverse event report form
	Pharmacists: pharmaceutical service directors at hospitals where the product is prescribed and dispensed	Pharmacy record form
	Patients	Patient booklet Patient card 15-08-2020
Voriconazole Voriconazol Hikma	**Physicians:** infectious diseases specialists, haematologists, dermatologists, oncologists	Q&A brochure Checklist
	Patients	Alert card 24-08-2020

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