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ADRs in the Literature
Latency times and frequency of selected adverse reactions to common vaccines

It is not usually easy to find systematized literature data on typical latency intervals that can be expected between vaccine administration and occurrence of significant adverse effects. Lack of this kind of temporal data can make it difficult to either confirm or rule out a causality nexus.
At a time when special attention has been given to the minimization of very rare but potentially serious adverse reactions to vaccines, revisiting a "classic" table published by the World Health Organization (adapted from "Supplementary information on vaccine safety Part 2: Background rates of adverse events following immunization") could be in order. This table lays out the frequency and run-in times of serious adverse effects following immunization with common vaccines that have been in use for many decades.

Vaccine	Reaction	Latency time	Frequency (per 1 million doses)
BGG	Suppurative lymphadenitis BCG osteitis Disseminated BCG-itis	2-6 months 1-12 months 1-12 months	100-1000 1-700 2
Diphtheria-Tetanus-Pertussis	Anaphylaxis/shock Persistent, inconsolable crying (>3 hrs) Hypotonic-hyporesponsive episode Seizures Encephalopathy	0-1 hour 0-24 hours 0-24 hours 0-3 days 0-3 days	20 1000-60,000 570 570 [a)] 0-1
Hepatitis B	Anaphylaxis Guillain-Barré syndrome	0-1 hour 1-6 weeks	1-2 5
Measles / MMR[b)]	Anaphylaxis Febrile seizures Thrombocytopenia	0-1 hour 5-12 days 15-35 days	1-50 333 33
Tetanus	Anaphylaxis Brachial neuritis Sterile abscess	0-1 hour 2-28 days 1-6 weeks	1-6 5-10 6-10

a) Seizures are mostly febrile. Their frequency depends on past history, family history and age, risk being significantly less in infants younger than 4 months.
b) Reactions (except anaphylaxis) do not supervene when the vaccinee is already immune (about 90% of those receiving a second dose). Febrile seizures are not likely in children older than six years.

• ***https://apps.who.int/iris/handle/10665/66675***

INDEX CARD

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Donepezil
cardiac conduction disorders including QT interval prolongation and torsade de pointes

Cholinergic inhibition can be associated with QT interval prolongation.
Donepezil is a centrally acting, specific and reversible acetylcholenisterase inhibitor, which is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's disease.

As part of a safety signal review that was concluded in July 2021 and which concerned cardiac conduction disorders, including QT interval prolongation and torsade de pointes, post-marketing and literature data, as well as ADR reports of cases of QT interval prolongation and torsade de pointes associated with the use of donepezil, were assessed. It was concluded that there is a reasonable possibility that a causal relation exists between donepezil and those undesirable effects. The PRAC at EMA has therefore recommended that the SmPCs of medicinal products containing donepezil include the following new information:

4.4. Special warnings and precautions for use
There have been post-marketing reports of QTc interval prolongation and Torsade de Pointes (see sections 4.5 and 4.8). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients treated with drugs affecting the QTc interval, or in patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.

4.5. Interaction with other medicinal products and other forms of interaction
Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil. Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring (ECG) may be required. Examples include:
- Class IA antiarrhythmics (e.g. quinidine)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)
- Certain antibiotics (e.g. clarithromycin, erythromycin, levofloxacin, moxifloxacin

4.8. Undesirable effects
Frequency not known: Polymorphic ventricular tachycardia including Torsade de Pointes; Electrocardiogram QT interval prolonged
[common: Accidents] including falls

Ana Isabel Severiano

What do they mean?

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

Excipients: safety information in patient leaflets – part 3

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Azo colouring agents	Oral	*May cause allergic reactions.*	• They include, for instance: Tartrazine (E102), Sunset yellow FCF (E110), Azorubine, Carmoisin (E122), Amaranth (E123), Ponceau 4R, Cochineal red A (E124), Brilliant black BN, Black PN (E151). • Many medicines look similar – colour, as well as shape and/or scoring, can facilitate identification and help to prevent errors. • Colour can help make a medicinal product more acceptable to the patient, or a formulation more uniform whenever one of its ingredients has an intrinsically variable aspect from batch to batch. By conferring greater opacity, colouring agents can also contribute to a product's stability when exposed to light.
Chlorocresol	Topical, parentheral	*May cause allergic reactions.*	• Used as an antimicrobial preservative in cosmetics and medicines; active against bacteria and fungi.
Cyclodextrins	All	*This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.* *Do not use in children less than 2 years old unless recommended by your doctor.*	• They can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. • There is insufficient information on effects in children less than 2 years old. • Based on animal studies and human experience, harmful effects are not expected at doses below 20 mg/kg/day.
	Oral	*Cyclodextrins may cause digestive problems such as diarrhoea.*	• High doses can cause reversible diarrhoea and cecal enlargement in animals.
	Parentheral	*If you have a kidney disease, talk to your doctor before you receive this medicine.*	• In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur. • In children less than 2 years, lower glomerular function may protect against renal toxicity; on the other hand, it can lead to higher blood levels.

To be continued ►

▶ *Cont´d*

Excipients: safety information in patient leaflets – part 3

Excipient	Route(s) of administration	Information in Patient Leaflet	Comments
Dimethyl sulphoxide	Topical	*May be irritant to the skin.*	• It has exceptional solvent properties, both for organic and inorganic compounds. It is highly hygroscopic and can absorb up to 70% of its weight in water.

Educational Materials published on the Infomed product information webpage

Click on the links

INN Medicinal product	Target	Materials? Online publication date
Delamanid *Deltyba*	**Healthcare professionals** **Patients**	Guide Guide 01-12-2021
Oxodotreótido de lutécio (^{177}Lu) *Lutathera*	**Doentes**	Leaflet 28-12-2021
Quetiapine *Quetiapina Aurobindo* *Quetiapina Aurovitas* *Quetiapina Generis*	**Physicians:** neurology, psychiatry, general/family medicine, internal medicine	Educational material for prescribers 06-12-2021

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