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# Adverse Drug Reaction (ADR) Reporting in COVID-19 Patients

**Read here** (in Portuguese) a Circular from the Board of Infarmed.

**Report here** any adverse drug reaction in patients with COVID-19, either concerning medicines used to treat the coronavirus infection or drugs administered to treat other concomitant or pre-existing conditions.

Remember to provide the following essential **data**:

- Patient data, including gender and age
- Whether infection has been confirmed through testing or diagnosis has been made presumptively based on clinical features
- ADR description
- Trademark name, active ingredient and batch number of the suspected medicinal product
- Dose and duration of treatment with the product
- Concomitant medicines
- Other health conditions

*From the Director*

## Portal RAM

Notificação de Reações Adversas a Medicamentos

**Report an adverse drug reaction here.**
**Find answers to your questions about the ADR Portal here.**

**INDEX CARD**

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# Thiazide, thiazide-like diuretics and combinations: risk of choroidal effusion

**Quick Read**

Due to the presence of a sulphonamide group, thiazide diuretics can be associated with the idiosyncratic occurrence of choroidal effusion of the eye. This can result in visual field changes, acute myopia or even acute closed angle glaucoma with risk of loss of vision.

*Drugs from the therapeutic class of thiazide, thiazide-like diuretics and combinations are recommended as first line therapy for hypertension and are indeed some of the most widely prescribed medicines the world over. Diuretic action occurs through inhibition of sodium chloride resorption in the initial stretches of the distal renal tubule. Choroidal and ciliary body effusion is an abnormal accumulation of fluid in the eye's suprachoroidal space. It is a common complication of glaucoma surgery and is also often associated with various conditions, including infectious and inflammatory conditions, trauma, neoplasms, venous congestion, and adverse reactions to drugs such as sulphonamides and their derivatives.*

Thiazide diuretics share a common structural sulphonamide group which accounts for their similar mode of action and incidence of adverse effects. Sulphonamide and its derivatives can cause an idiosyncratic reaction arising from an eicosanoid metabolism (prostaglandin-thromboxane) imbalance which results in increased transudation through the eye's choroidal capillaries.

A ciliary body effusion can cause a defect in the visual field, acute myopia and even acute closed angle glaucoma, with an attending risk of permanent loss of vision. Symptoms include sudden onset of decreased visual acuity or ocular pain and they usually supervene from a few hours to weeks after the start of therapy. Risk factors for the development of acute closed angle glaucoma can include a history of sulphonamide or penicillin allergy.

Following confirmation of a safety signal concerning choroidal effusion in patients on thiazide or thiazide-like diuretics, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) conducted a review of every available case from the European adverse drug reaction database (EVDAS) and the literature. The results of this review provided the rationale for changes to the texts of the Summary of the Product's Characteristics (SPC) and Patient Information Leaflet (PL) of those medicines. The SPCs will therefore include the following:

**4.4. Special warnings and precautions for use**

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. […]

**4.8. Undesirable effects**

➔ For hydrochlorothiazide-, chlortalidone- and indapamide-containing products:

Eye disorders: choroidal effusion (frequency not known)

➔ For bendroflumethiazide, cicletanine, clopamide, cyclopenthiazide, hydroflumethiazide, metipamide, metolazone, xipamide-containing products (choroidal effusion has not yet been reported but is considered a class effect) […]

Cases of choroidal effusion with visual field defect have been reported after the use of thiazide and thiazide-like diuretics.

*Adriana Gamboa*

## Communications to Healthcare Professionals published in the Infomed product information webpage

**Click on the links.**

| INN<br>Medicinal product | Target | Comunication<br>Online publication date |
|---|---|---|
| **Amoxicillin + clavulanic acid**<br>Amoxicilina + Ácido Clavulânico Sandoz (pó para suspensão oral) | **Pharmacists:** community | Updated oral suspension powder vial preparation<br>08-04-2020 |
| **Bacillus Calmette-Guérin**<br>BCG-Medac | **Physicians:** oncologists and urologists who treat patients with non-invasive urothelial bladder carcinoma<br>**Pharmacists:** hospital<br>**Nurses:** who may handle and/or administer the product | Implementation of the Patient's Alert Card on risk of reactivation of latent BCG infections<br>15-04-2020 |
| **Ciproterone**<br>Products contining ciproterone acetate only | **Physicians:** dermatologists, endocrinologists, gynaecologists, GPs/family doctors, urologists, oncologists and psychiatrists | Use restrictions due to risk of meningioma<br>15-04-2020 |

*Compiled by Patrícia Catalão*

## Educational Materials published in the Infomed product information webpage

**Click on the links.**

| INN<br>Medicinal product | Target | Comunication<br>Online publication date |
|---|---|---|
| **Asfotase alfa**<br>Strensiq | **Patients** | Autoinjection guide<br>Injection guide for parents and guardians<br>03-04-2020 |
| **Bacillus Calmette-Guérin**<br>BCG-Medac | **Patients** | Alert card<br>16-04-2020 |
| **Pembrolizumab**<br>Keytruda | **Patients** | Information brochure<br>Alert card<br>20-04-2020 |
| **Rituximab**<br>Rixathon | **Physicians:** rheumatologists and internists | Guide – non-oncological indications |
| | **Patients** | Brochure – non-oncological indications<br>07-04-2020 |
| **Rivaroxaban**<br>Xarelto | **Physicians:** cardiologists, orthopaedic surgeons, internists, GPs and vascular surgeons | Prescriber's guide<br>28-04-2020 |
| **Sodium oxybate**<br>Xyrem | **Physicians:** prescribers | Treatment start form |
| | **Patients** | Administration instructions<br>Alert card<br>Frequently asked questions<br>28-04-2020 |

*Compiled by Patrícia Catalão*

# Recommended duration of contraception following discontinuation of treatment with a genotoxic product

In order to minimize the risk of genetic damage caused by genotoxic drugs and to ensure the genetic integrity of gametes at conception, high effectiveness contraception is usually recommended during treatment, as well as for a period of time afterwards. The European Medicines Agency (EMA) Safety Working Party has produced a document to respond to specific questions around this matter and to provide a rationale for harmonization within the EU of recommendations in the Summaries of the Products' Characteristics.

These recommendations apply to any substance irrespective of therapeutic indication and not only to antineoplastic agents. In every case, other factors should be taken into consideration such as concomitant medicines, dosing and treatment duration.

**For how long is contraception recommended following treatment with a genotoxic drug?**

## Women

Ovaries contain at any given time a great number of follicles at varying stages of development (folliculogenesis). This is essential for fertility. For each primordial follicle the process begins with recruitment into the group of growing follicles and ends with ovulation or natural cell death by atresia. Around six months are needed for an oocyte to mature all the way to the stage of a Graafian follicle that is "ready" for ovulation.

Studies in animals have demonstrated that oocytes that have been exposed to genotoxic substances at the initial stages of maturation produce foetal malformations, whereas later exposure at the pre-ovulation stage tends to be associated with spontaneous miscarriage.

Contraception after the end of therapy with a genotoxic drug should therefore go on for six months in order to cover for all the stages of folliculogenesis and to ensure that most potentially affected oocytes will have been naturally eliminated through atresia. To this time interval another period needs to be added corresponding to relevant systemic exposure to the drug's metabolites, which is estimated to be of around five half-lives. Hence: **5 half-lives of the medicinal product + 6 months**.

In the rather more theoretical case of pure aneugenic drugs (i.e. drugs that only induce an abnormal number of chromosomes from cell division) it should be sufficient to add one month to five half-lives, since this type of drugs are supposed to only affect oocytes re-entering meiosis.

## Men

Germ cell susceptibility to DNA damage depends on their developmental stage, from spermatogenesis in the testes to sperm cell maturation in the epididymis. At the initial stages exposure of spermatogonia to chemotherapeutic agents results in their elimination or in reparable DNA damage. However, in later maturation phases (spermatocytes, spermatids) both cell death and genetic material repair become less likely. Repair is impossible at the mature gamete stage.

Considering that the process of spermatogenesis extends itself for 60 to 75 days and that another 10 to 14 days are necessary for the transfer of sperm to the epididymis, effective contraception should go on for **5 half-lives of the medicinal product + 90 days**.

You can look up further details regarding these recommendations **here**.

*From the Editor*