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Pneumorel® and Pneumorel retard®: revoked

Quick Read
On account of potentially life-threatening arrhythmia, Pneumorel® and Pneumorel retard® (fenspiride) have been withdrawn from the market.

Fenspiride is an antitussive and expectorant agent with anti-bronchoconstrictive and anti-inflammatory properties. It acts through various mechanisms: H1 histamine receptor antagonism, papaverine-type spasmolysis, reduction of the production of proinflammatory factors. It was indicated in upper and lower respiratory conditions. The only cardiovascular adverse effects previously listed had been palpitations/tachycardia and hypotension.

The Marketing Authorisations of medicinal products containing fenspiride have been revoked as the result of a European safety data review. All available evidence was taken into account, including reported cases of **QT interval prolongation and torsades de pointes**, lab tests, published literature and stakeholder contributions. The cases reported and the non-clinical studies did indeed show that fenspiride has proarrhythmic potential.

Since cardiac rhythm problems can be serious and supervene without warning, patients at risk cannot be pre-emptively identified, and fenspiride was indicated merely for non-serious symptoms (cough and sputum), the Pharmacovigilance Risk Committee (PRAC) has concluded that these products' **benefit-risk balance for the approved indications is now unfavourable**. As a consequence, marketing of fenspiride-containing products has ceased.

In Portugal the Marketing Authorisations of *Pneumorel xarope 2mg/ml e Pneumorel retard comprimidos gastrorresistentes 80 mg* have been revoked; they had been suspended earlier on 12-02-2019 and withdrawn from the market.

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INDEX CARD

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Safety of antirheumatic medicines in pregnancy

Systemic rheumatic disease encompasses a broad spectrum of conditions, namely systemic lupus erythematosus (SLE), antiphospholipid syndrome, rheumatoid arthritis, systemic sclerosis and systemic vasculitides. Autoimmunity can affect fertility and pregnancy. The conflict of interests between maternal needs and foetal well-being is a real pharmacotherapeutical challenge when approaching those conditions during pregnancy.

With the advent of new drugs most women with rheumatic conditions can now contemplate pregnancy. Inspite of recent breakthroughs available data concerning immunosuppressive drugs and pregnancy have been accumulating only slowly and piecemeal (Table 1).

Table 1. Toxicity of non-biological anti-rheumatic therapy in humans.

Drug	Effects on parents	Effects on foetus
Aspirin / NSAID	None	Premature closure of the arterial duct (discontinue in the 3rd trimester)
COX-2 inhibitors	None	Unknown
Sulfasalazine	None	Cleft palate; VSD; Coarctaton of the aorta (but considered safe during pregnancy)
Glucocorticoids	PRM Hypertension Glucose intolerance Osteoporosis Osteonecrosis	SGA; Adrenal hypoplasia; Promotes pulmonar maturation; Cleft palate^{+}; Stillborn^{+}
Azathioprine	PRM	SGA; D category but used in post-transplant patients
6-mercaptopurine	*	SGA; Prematurity; IUGR; Cleft palate; Literature on IBD suggests it is safe
Ciclosporin A	Kidney failure	SGA; Used in pregnant post-transplant patients
Mycophenolate mofetil	*	Clinical case study reports of short 5th finger and other abnormalities (contraindicated in pregnancy).
Methotrexate	*	Embryotoxicity; Skeletal abnormalities; Facial abnormalities
Leflunomide	*	Embryotoxicity
Cyclophosphamide	Decreased fertility in both men and women	Teratogenic (contraindicated)

* *No data available.*

$^{+}$ *Theoretical risk or decribed in clinical case studies only.*

COX: cyclooxygenase; IBD: inflammatory bowel disease; IUGR: intrauterine growth restriction; NSAID: nonsteroidal anti-inflammatory drug; PRM: premature rupture of membranes; SGA: small for gestational age; SLE: systemic lupus erythematosus; VSD: ventricular septal defect.

Source: Bermas B (2010) Management of rheumatologic disorders during pregnancy.

In 2016 the **European League Against Rheumatism (EULAR)** set up a task force to reach a consensus on drugs used in rheumatic conditions and their indications in pregnancy (Table 2). These recommendations brought about a consensus in a controversial but crucial field in rheumatology. However, inspite of multiple international efforts, evidence on the safety of a substantial number of medicines used in pregnancy is still limited, and further research is needed.

Table 2. 2016 EULAR recommendations on the use of anti-rheumatic drugs during pregnancy

To consider when using anti-rheumatic drugs in pregnancy	Recommendation grade†
csDMARDs‡ acceptable in pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued during pregnancy for sustained remission or for the treatment of disease flares.	B
csDMARDs‡ considered to be **teratogenic** are methotrexate, mycophenolate mofetil and cyclophosphamide – they should be suspended before pregnancy.	B
NSAIDs and prednisolone should be considered in pregnancy, if necessary, fto control active disease symptoms. NSAIDS should be used in the first and second trimester only.	B
Pulses of methyprednisolone, intravenous immunoglobulin or even cyclophosphamide should be considered in the first or second trimester, in the case of severe or refractory disease.	B
csDMARDs‡, tsDMARD§ and anti-inflammatory agents with insufficient data on use during pregnancy should be avoided until further evidence becomes available. This applies to leflunomide, tofacitinib and to selective COX II inhibitors.	B-D
Of the bDMARDs¶, continuing therapy with tumour necrosis factor (TNF) inhibitors should be considered in the earlier stages of pregnancy. Etanercept and certolizumab can be considered throughout the gestation given their low rates of transplacental transference.	B
bDMARDs¶ (rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab) with scarce pregnancy safety data should be replaced before conception by other drugs. They should be used in pregnancy only when maternal disease cannot be effectively controlled by any other drugs that are safer during pregnancy.	D

† Grade A: Class I evidence from meta-analyses of controlled, randomized studies or from at least one controlled, randomized study. Grade B: Class II evidence from at least on controlled, non-randomized study or from at least one quasi-experimental study or from extrapolation from class I recommendations. Grade C: Class III evidence from descriptive studies such as comparative studies, correlation studies or case-control studies, or from extrapolation from class I and II recommendations. Grade D: Class IV evidence from expert consensus, from specialist opinion and/or clinical experience, or from extrapolation from class II or III recommendations.

‡ Conventional synthetic disease modifying anti-rheumatic drugs.

§ Targeted synthetic disease modifying anti-rheumatic drugs.

¶ Biological disease modifying anti-rheumatic drugs.

In conclusion, effective pharmacological treatment of active inflammatory rheumatic conditions is possible to achieve with a reasonable degree of safety for the foetus. To this end, good pre-conceptional control of disease activity is necessary.

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Portuguese Pharmacovigilance E-book

In Chapter 7.2. Cardiovascular Adverse Reactions (Pedro Marques da Silva)

Cardiovascular adverse reactions often mirror the pharmacodynamic characteristics of the drug and of the indication condition. This chapter focusses mostly on typical clinical practice situations: drug-induced pro-arrhythmic effects (including detection and assessment guidelines), the cardiotoxic pleiotropism of antineoplastic agents, high blood pressure caused by drugs, and the cardiovascular safety of oral antidiabetic agents (and of insulin).

To read more online or download the E-book click here

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	Patients	Alert card 18-07-2019
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Compiled by Magda Pedro