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Editor's Notes

Interaction between implantable medical devices and other medical devices used for diagnostic or therapeutic purposes may cause serious problems in patients as well as damage and malfunction in the devices themselves. It is imperative that health professionals be well aware of the need to prevent this type of incidents. The recommendations included in this issue's centre page article have previously been published in extended version in an information brochure from the Infarmed Health Product Vigilance Department. They aim to contribute towards the safe use of diagnostic and therapeutic devices in patients carrying implantable devices.

The Boletim's index is now online, and can be searched by medicinal product or pharmacotherapeutic group, from the year 2000 onwards. As yet it is available in Portuguese only at:
http://www.infarmed.pt/portal/page/portal/INFARMED/PUBLICACOES/TEMATICOS/BOLETIM_FARMACOVIGILANCIA/INDICE_REMISSIVO

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians),* **purple** *(pharmacists)* **or white** *(nurses)*

Also online at:
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Salbutamol and risk of myocardial ischaemia

Use in obstetrics for premature delivery control

- Contraindicated in patients with previous ischaemic heart disease (IHD), or with significant risk factors for IHD.
- Use with caution in women in premature labour – cardiac and respiratory functions, including ECG, should be monitored.
- Discontinue therapy should any signs of myocardial ischaemia supervene, such as chest pain or ECG changes.

Use in respiratory disease

- Patients with severe underlying heart disease (e.g., IHD, arrhythmia, or severe heart failure) who are undergoing treatment with salbutamol should be advised to seek medical care in case of chest pain or other symptoms of possible worsening of their cardiac condition.
- Special attention should be paid to the occurrence of symptoms such as dyspnoea and chest pain, in that they may be of respiratory or cardiac origin.

Madalena Arriegas

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	European Medicines Agency
IL	Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

INDEX CARD | **Director:** Regina Carmona **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Alexandra Pêgo, Ana Araújo, Catarina Martins, Eugénio Teófilo, Fátima Bragança, João Ribeiro Silva, Madalena Arriegas, Paula Roque, Pedro Marques da Silva, Regina Carmona, Susana Gonçalves, **Advisory Board:** Vasco Maria, Luísa Carvalho, Helder Mota Filipe (INFARMED Executive Board); INFARMED Medicines Evaluation Committee. **Publisher:** INFARMED-Instituto Nacional da Farmácia e do Medicamento, Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, correio elertrónico: infarmed@infarmed.pt **Design and Prodution:** nsolutions - design e imagem, lda. **Printing:** Tipografia Peres **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 40.000

Interactions between implantable medical devices and medical devices used for therapy or diagnosis

Several cases of **serious injury** including burns, coma, and permanent neurological deficit in patients carrying implants who were submitted to certain diagnostic or therapeutic manoeuvres, have been published in both official health authority databases and scientific journals.[1,2,3] The **risk of interaction** between implantable medical devices and other medical devices used for diagnostic or therapeutic purposes depends on many factors, namely electromagnetic interference, radiofrequency, and electrical conductivity.[2,4-7] These interactions may cause both serious injury in **patients** and damage to the **devices** proper which may then cease to **function** as intended. Various authors have pointed out that **raising awareness** of the risks associated with using and handling these devices strongly contributes towards preventing undesired incidents. Health services should set up measures to **ensure good practices** in order to **prevent incidents** associated with diagnostic and therapeutic procedures.

Health professionals should be warned about the risk of interactions between the various medical devices and systems. The following recommendations intend to contribute to a safer use of medical diagnostic and therapeutic devices in patients with implants. They address especially:

- Radiology physicians
- Radiology technologists
- Nurses

These recommendations refer namely to:

- Active implantable medical devices and systems containing non-ferrous materials (aluminium, titanium and carbon composites):

- Cardiac stimulators
- Cardiac defibrillators
- Neurostimulators
- Hearing devices
- Clips used in cerebral aneurysm surgery
- Stents
- Heart valves
- Intrauterine devices
- Transdermal drug delivery systems (hormones, nitroglycerin, nicotine, etc.)

- Medical diagnostic and therapy devices:

- Ultrasound, shortwave and microwave diathermy
- Ultrasonography
- Electrosurgery (e.g., electrical scalpel)
- External defibrillator
- Magnetic resonance (MR)
- X-ray devices
- Radiotherapy devices
- Lithotripsy or ultrasound therapy devices

Given the diversity and complexity of the above medical devices and systems, the recommendations herein cannot encompass every single possible clinical scenario: only the more frequent and higher risk interactions are therefore listed.

Interaction between Magnetic Resonance and Drug Delivery Transdermal Systems[1]

Drug delivery transdermal systems are stick-on plasters/patches that deliver drugs through the skin in a controlled way for a given period of time. Since they actually are reservoirs of medicinal products, **some of these systems** include **aluminium, titanium or carbon composite components**. Although these materials are non-ferrous metals which are theoretically compatible with MR (they are not attracted by the MR system's static magnetic field), they do conduct electricity. Therefore, when placed within the range of a radiofrequency wave field produced by the MR system, the electrical current generated is enough to cause excessive heating of tissues and consequently **discomfort, burns, or imaging problems**.

In Portugal, medicinal products with marketing authorisation whose drug reservoir contains aluminium, titanium or carbon composites are:

- Flector Tissugel® (Diclofenac hydroxyethylpyrrolidine) - Laboratórios Delta
- NiQuitin CQ® (Nicotine, 7 mg) – GlaxoSmithKline Consumer Healthcare
- NiQuitin CQ® (Nicotine, 14 mg) – GlaxoSmithKline Consumer Healthcare
- VNiQuitin CQ® (Nicotine, 21 mg) - GlaxoSmithKline Consumer Healthcare
- Transact Lact, 40 mg® (Flubiprofen) – Abbott Laboratórios

Interaction between diathermy and metallic implants[5]

Diathermy therapy consists of generating heat in tissues by means of high-frequency electrical current. Excessive heating destroys tissues by electrocoagulation. For this reason, radiofrequency diathermy, microwave diathermy and, under certain circumstances, ultrasound diathermy too, are all contraindicated in patients with active or non-active medical implant devices containing **metallic components**. Interaction between the energy released by the diathermy device and the implant's metallic component (even if it is just a small-sized fragment left in the body after explantation) can cause excessive heating of the tissues surrounding the device and result in **serious injury or death**. Diathermy can furthermore cause implanted systems to malfunction.

Interaction between magnetic resonance and active neurological implants[2]

Various international sources, including the Food and Drug Administration (FDA), describe the occurrence of **serious injury (death, coma, permanent neurological deterioration)** in patients with implanted neurological stimulators (deep brain, vagal nerve, spinal cord, peripheral nerve, or neuromuscular stimulation) who underwent magnetic resonance imaging procedures. Heating of the electrodes at the tip of the metal wire causing injury to surrounding tissues was the probable mechanism underlying those cases. The electrode's configuration, the type of radiofrequency coil, and the rate of specific absorption, seem to be other factors strongly influencing local electrode tip temperature increase.[6]

It is therefore recommended that patients with **active implantable devices** should be strictly prohibited to undergo any magnetic resonance imaging exams. The same applies to patients with **pacemakers**. **However**, recent studies have shown that the risk associated with MR in patients with bone fusion stimulators and some infusion pumps is minimal.[6]

The following **Table** summarises the main recommendations issued by the French (Afssaps) and Canadian (Health Canada) authorities[4,5,7]:

	Implantable pacemaker	Implantable defibrillator	Implantable Neurostimulator
Shortwave and microwave diathermy	**Absolute contraindication**	**Absolute contraindication**	**Absolute contraindication**
Ultrasound diathermy	Caution	Caution	**Absolute contraindication**
Electromagnetic stimulation devices	Caution	Caution	**Absolute contraindication**
Magnetic resonance	**Absolute contraindication**	**Absolute contraindication**	**Absolute contraindication**
Electrosurgery devices	Caution	Caution	Caution
External defibrillator	Caution	Caution	Caution
Radiotherapy devices	Caution	Caution	Caution
Lithotripsy or ultrasound devices	Caution	Caution	Caution
Fluoroscopy or other X-ray devices	No restrictions	No restrictions	No restrictions
Ultrasonography	No restrictions	No restrictions	No restrictions

Bearing these recommendations in mind, health professionals should systematically:

- *Conduct a thorough clinical assessment of the patients before the diagnostic procedure is carried out, in order to look for the contraindications and special precautions indicated above.*
- *Assess the risk-benefit ratio of the procedure and consider alternative methods in those cases where caution is advised. If necessary, contact should be made with the practitioner who implanted and is following up on the medical device, or with the device's actual manufacturer.*
- *Screen the patients through a list of specific questions (*) and recommendation of use (**). It is particularly important to observe the manufacturer's instructions for use.*
- *A radiological exam should be performed previous to diathermy or MR to look for metallic fragments that may cause the above-described adverse effects.*
- *Deactivate any active implantable medical devices, if at all possible.*
- *Use the diagnostic or therapeutic device in an acceptable way but with its minimum effective capacity.*
- *Monitor (whenever necessary) the patient's vital signs throughout the medical procedure.*
- *Immediately discontinue the procedure in case an incident occurs.*
- *Check that the active implantable medical device is functioning during and after the medical procedure.*

(*) List of products that should be included in the questionnaire (essentially for MR procedures):

- *Active implantable medical devices (pacemakers, defibrillators, neurostimulators, cochlear implants, infusion pumps)*
- *Transdermal drug delivery systems*
- *Coloured contact lenses*
- *Stents, bone screws*
- *Intrauterine devices containing copper*
- *Metallic heart valve*
- *Cervical traction halos*
- *Metallic fragments in the body (e.g., due to explantation of metallic medical device)*
- *Permanent tattoo/eyeliner (in case it contains metallic components)*

(**) Recommendation – Do not wear during magnetic resonance imaging procedures:

- *Objects in pockets*
- *Jewellery (including piercing)*
- *Glasses*
- *Metallic hair ornaments*
- *Clothes with metallic components*
- *Eyeliners with metallic components*
- *Coloured contact lenses*
- *Metallic dentures*

Incident reporting

It is essential that health professionals report any incidents associated with medical devices. Reporting forms are available at the INFARMED site at:

http://www.infarmed.pt/portal/page/portal/INFARMED/MONITORIZACAO_DO_MERCADO/VIGILANCIA_DE_DISPOSITIVOS_MEDICOS

Any incident or risk of serious incident associated with the use of medical devices should be reported to INFARMED to:

Instituto Nacional da Farmácia e do Medicamento

Departamento de Vigilância de Produtos de Saúde

Parque de Saúde de Lisboa, 53, Pav. 17 A, 1740-004 LISBOA

Ph: 21 797 7145 Fax: 21798 7367
Email: dvps@infarmed.pt

Adriana Gamboa

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Epoetins – Safety information review

Epoetins are used in the treatment of anaemia in patients with chronic renal failure and in cancer patients with non-myelogenous malignancies undergoing chemotherapy.

All epoetins are being submitted to a Europe-wide safety assessment triggered by new data suggesting that there could be an **increased risk of serious cardiovascular complications** in chronic renal failure patients, and a possible increase in **tumour progression** in cancer patients. INFARMED meanwhile **recommends**:

- Epoetins should only be used in accordance with the **therapeutic indications** (section 4.1) and **posology and method of administration** (section 4.2) stated in the approved SPC.
- Regarding the treatment of **patients with chronic kidney failure**, there is evidence that **haemoglobin concentrations higher than 12 g/dl** are associated with **increased risk of serious cardiovascular morbidity and mortality**. Physicians should bear this in mind when considering aiming for haemoglobin concentrations higher than 12 g/dl.
- There is some evidence that epoetins may be associated with **increased morbidity and mortality** when used in patients with **solid tumours** who are **not** undergoing **chemotherapy**.
- Patients should be carefully monitored in order to ensure that the **lowest dose** of epoetin necessary for adequate control of anaemic symptoms is used.

Telithromycin 400 mg
Restriction to indications, new contraindication, and reinforcement of safety measures

EMEA has been reviewing the safety and efficacy aspects of telithromycin Ketek® since 2006. Several updates to the safety information of this medicinal product have followed, which included a reinforcement of warnings on **serious hepatic reactions** and a contraindication of use in patients with a past clinical history of liver condition. More recently, EMEA has concluded that the use of Ketek® is associated with a higher risk of **worsening of myasthenia gravis**, **loss of consciousness**, and **self-limited visual disturbances.**

The **therapeutic indications** of this medicine have been restricted and its SPC updated: Ketek® should be used in cases of acute exacerbation of chronic bronchitis and in acute sinusitis caused by bacterial strains suspected or confirmed to be resistant to beta-lactamic antibiotics and/or macrolides (according to the patient's clinical condition, or national and/or regional resistance data) but which are covered by telithromycin's antibacterial spectrum. Additionally, Ketek® should be used in tonsillitis/pharyngitis, i.e., in the treatment of infections caused by *Streptococcus pyogenes*, as an alternative when beta-lactamic antibiotics are not appropriate, in countries or regions with significant prevalence of macrolide-resistant *S. pyogenes* whose resistance is mediated by *erm*TR or *mef*A.

- **Myasthenia gravis** has been changed from a "Warning and special precaution of use" to a "**Contraindication**".
- The safety information concerning visual disturbance and loss of consciousness has been reviewed in order to underscore the recommendations on **driving vehicles and heavy machinery**. A new recommendation to **take the medicine at bedtime** has also been included.

Medicinal Plants from A to Z
described adverse reactions

- **Echinacea, purple coneflower** *(Echinacea purpurea)*
  - hypersensitivity (especially in subjects with allergy to Asteraceae, a family of daisy-like flower plants)
  - mild nausea, other GI symptoms
  - exacerbation of autoimmune and systemic disease in general (??)

Nº of Medline citations: 28
Main uses described: common cold

- **Lemon balm, melissa** *(Melissa officinalis)*
  - skin irritation (topical use)

Nº of Medline citations: 9
Main uses described: sedative, antispasmodic, healing (herpes simplex)

- **St John's wort** *(Hypericum perforatum)*
  - dry mouth
  - dizziness
  - constipation, other GI symptoms
  - photosensitivity
  - induction of mania
  - decreased effect and/or serum levels of: theophylline, warfarin, digoxin, cyclosporin, HIV protease inhibitors, oral contraceptives

Nº of Medline citations: 29
Main uses described: antidepressant

- **Yerba mate** *(Ilex paraguariensis)*
  - risk factor for oropharyngeal cancer (??)

Nº of Medline citations: 3
Main uses described: stimulant, diuretic

NB 1: The main uses are those most frequently described in the literature irrespective of evidence of effectiveness. Their presentation herein is factual and does not mean that therapeutical uses mentioned are approved or implicitly condoned in any way by this publication.
NB 2: The number of Medline citations is merely intended to give an idea of the magnitude of publications on adverse reactions associated with the product. Key-words used: "human side effects", "toxicity in humans", "adverse reactions".

What should one report?

Every suspected serious adverse reaction, even if already previously described. Seriousness criteria include:

- causing death
- life threatening
- prompting hospital admission
- prolonging hospital stay
- resulting in persistent or significant incapacity
- suspected congenital anomaly or malformation
- does not meet any of the above criteria but health professional considers it to be a serious ADR

Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)