

Drug Safety Update



Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

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The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.



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www.evidence.nhs.uk/

In our first article this month, note advice about misoprostol vaginal delivery system (Mysodelle) following a routine review, which highlighted reports of uterine tachysystole, some of which did not respond to tocolytic treatment (page 2). Monitor patients closely and remove the vaginal delivery system immediately if there are excessive or prolonged uterine contractions, if there is concern for mother or baby, or at the onset of labour.

Next, read amended contraception advice for male patients taking mycophenolate medicines to prevent transplant rejection (page 3). As a precautionary measure, it is now recommended that either male patients **or** their female partner use reliable contraception during treatment with mycophenolate medicines and for at least 90 days after stopping (it was previously advised that both men receiving treatment and their female partners should use contraception to prevent pregnancy). Female patients of childbearing potential receiving mycophenolate medicines should always use contraception.

Finally, we update you as to the status of gadolinium-containing contrast agents after our previous article in the December 2017 issue of Drug Safety Update. Omniscan and intravenous Magnevist are no longer authorised for use and a product recall of existing unexpired stock is underway (page 5).

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Misoprostol vaginal delivery system (Mysodelle): reports of excessive uterine contractions (tachysystole) unresponsive to tocolytic treatment

Monitor patients closely and remove the vaginal delivery system immediately in cases of excessive or prolonged uterine contractions, at the onset of labour, or if there is clinical concern for mother or baby.

Advice for healthcare professionals:

- Mysodelle can cause uterine tachysystole that may not respond to tocolytic treatment
- monitor patients closely and remove the vaginal delivery system immediately if any of the following apply:
 - tachysystole: more than 5 contractions in a 10-minute window, averaged over a 30-minute window
 - prolonged contractions: single contractions lasting 2 minutes or longer
 - hypertonic contractions: contractions that are too frequent and a high resting tone in the uterus
- also remove the vaginal delivery system in the following instances:
 - there is a clinical concern for the mother or baby
 - onset of labour: rhythmic, firm contractions of adequate quality associated with cervical change, and/or at the latest when cervical dilation is 4 cm
 - when 24 hours have elapsed since insertion
- be prepared to administer tocolytic therapy; should this be needed, it can be administered immediately after removal of Mysodelle

Risk of tachysystole

[Misoprostol \(Mysodelle\) vaginal delivery system](#) is authorised for induction of labour in women with an unfavourable cervix, from 36 weeks' gestation, in whom induction is clinically indicated.

A routine EU review of Mysodelle investigated reports from a study¹ in which 13% of women (90 of 678 patients) randomly assigned to the 200-mg misoprostol vaginal insert developed uterine tachysystole requiring intervention. In 5 cases (0.7% of women), uterine tachysystole did not subside with the use of tocolysis.¹

Uterine tachysystole has been associated with poor uterine placental perfusion leading to a decrease in foetal oxygenation and eventually foetal compromise. In the study, despite the higher incidence of tachysystole requiring intervention recorded in women given the misoprostol vaginal insert than those given a dinoprostone vaginal insert (13% versus 4%, respectively), neonatal outcomes did not appear to differ.¹

The EU routine review of these cases concluded that uterine tachysystole that may not respond to tocolytic treatment can be caused by Mysodelle, even when used in accordance with the product information. The product information for Mysodelle has been updated to reflect this finding, and with actions to take to ensure that this risk is adequately managed. A [letter](#) was also sent to alert relevant healthcare professionals.

Call for reporting

Please continue to report suspected adverse drug reactions to misoprostol on a [Yellow Card](#).

Article citation: Drug Safety Update volume 11 issue 7; February 2018: 1.

[Mysodelle Summary of Product Characteristics.](#)

1. Wing DA, et al. [Misoprostol vaginal insert and time to vaginal delivery: a randomized controlled trial.](#) *Obstet Gynecol* 2013; 122: 201–09.

Direct Healthcare Professional Communication. [Misoprostol vaginal delivery system \(Mysodelle\).](#) 8 January 2018.

Mycophenolate mofetil, mycophenolic acid: updated contraception advice for male patients

Mycophenolate mofetil and its active metabolite mycophenolic acid, both used to prevent transplant rejection, are teratogenic and genotoxic. The available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, but there is insufficient evidence to rule out any risk. As a precautionary measure for male patients, it is now recommended that either the patient **or** their female partner use reliable contraception during treatment with mycophenolate medicines and for at least 90 days after stopping. Female patients of childbearing potential receiving mycophenolate should always use contraception.

Advice for healthcare professionals prescribing mycophenolate to male patients:

- available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, however mycophenolate mofetil and mycophenolic acid are genotoxic and a risk cannot be fully excluded.
- it is therefore recommended that male patients **or** their female partner use reliable contraception during treatment and for at least 90 days after stopping mycophenolate medicines
- discuss with male patients planning to have children the implications of both immunosuppression and the effect of prescribed medications on the pregnancy

Reminder for healthcare professionals prescribing mycophenolate to female patients:

- mycophenolate medicines remain contraindicated in women of childbearing potential who are not using reliable contraception and in pregnant women unless there are no suitable alternatives to prevent transplant rejection
- female patients of childbearing potential must use at least one reliable form of contraception before and during treatment and for 6 weeks after stopping mycophenolate medicines; 2 forms of contraception are preferred
- report suspected adverse drug reactions associated with mycophenolate medicines, including adverse pregnancy outcomes, to us on a [Yellow Card](#)

Background to teratogenic and genotoxic risk

Mycophenolate (mycophenolate mofetil and mycophenolic acid), authorised to prevent transplant rejection, is a major human teratogen known to cause miscarriages and congenital malformation in pregnant women. Between 45% and 49% of cases of exposure to mycophenolate in pregnancy result in miscarriage, and between 23% and 27% result in malformations (see below for reminder of pregnancy prevention advice for female patients).

Mycophenolate medicines are also genotoxic. Mycophenolate medicines are excreted in the semen, raising concerns regarding pregnancies exposed via the father. In [December 2015](#), based on a review of evidence at the time, we advised that men receiving treatment and their female partners should both use contraception to prevent pregnancy.

Male patients – review of risks associated with pregnancies exposure via the father

Following an in-depth routine review in Europe of all the available non-clinical and clinical data for men fathering children while receiving mycophenolate mofetil and mycophenolic acid, [recommendations to prevent pregnancy](#) have been updated.

Although the amount of mycophenolate present in semen has not been determined precisely, calculations based on animal data show that the maximum amount of mycophenolate that could be transferred to a woman is low and is unlikely to have any teratogenic effect. However, mycophenolate has also been shown to be genotoxic in animal studies, albeit at concentrations higher than the human therapeutic exposure levels, and the risk of genotoxic effects on sperm cells cannot be completely excluded. The available clinical evidence, while reassuring, is currently insufficient to rule out any risk in humans.

It is therefore recommended that, as a precautionary measure, either male patients **or** their female partners use reliable contraception and that men planning to have children discuss this with their doctor. The previous recommendation for men receiving treatment, specifying both the male patient and their partner use contraception, is no longer considered necessary. The clinical situation is continually monitored and, as more data becomes available, advice may be updated.

Female patients – reminder of pregnancy-prevention advice

In female patients the risk of serious birth defects and increased spontaneous abortion remains high (see [December 2015 Drug Safety Update](#)). The 2015 review of worldwide cases of congenital malformations after exposure during pregnancy confirmed mycophenolate mofetil as a powerful human teratogen, and showed evidence of an increased rate of congenital malformations and spontaneous abortions compared with other immunosuppressants.

In the literature,^{1,2,3} the risk for malformations associated with the use of mycophenolate is reported to be between 23% and 27% of livebirths, compared with 4–5% for female organ transplant recipients in the USA receiving immunosuppressants other than mycophenolate. For spontaneous abortions, the reported risk is between 45% and 49%, whereas the risk in organ transplant recipients receiving immunosuppressants other than mycophenolate varies between 12% and 33%, according to the type of immunosuppressant and type of transplanted organ.

Mycophenolate medicines remain contraindicated in women of childbearing potential who are not using reliable contraception. These medicines are also contraindicated in pregnant women unless there are no suitable alternatives to prevent transplant rejection.

Female patients of childbearing potential must use at least one reliable form of contraception before and during treatment and for 6 weeks after stopping treatment. Two forms of contraception are preferred. Mycophenolate treatment should only be initiated in women of childbearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy. Two pregnancy tests 8–10 days apart are recommended.

1. Sifontis NM, et al. [Pregnancy outcomes in solid organ transplant recipients with exposure to mycophenolate mofetil or sirolimus](#). *Transpl* 2006; 82: 1698–702.

2. Coscia LA, et al. [Report from the National Transplantation Pregnancy Registry \(NTPR\): outcomes of pregnancy after transplantation](#). *Clin Transpl* 2009: 103–22.

3. Hoeltzenbein M, et al. [Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services](#). *Am J Med Genet A* 2012; 158A: 588–96.

Physicians should ensure that female patients taking mycophenolate mofetil and mycophenolic acid understand:

- the risk of harm to a baby
- the need for effective contraception
- the need to plan for pregnancy and change treatment as necessary
- the need to immediately consult a physician if there is a possibility of pregnancy

Report suspected adverse drug reactions

Suspected adverse drug reactions associated with mycophenolate medicines, including adverse pregnancy outcomes, should be reported on a [Yellow Card](#).

Further information

- European Medicines Agency. [Mycophenolate: updated recommendations for contraception for men and women](#). 15 December 2017
- [Direct Healthcare Professional Communication. Mycophenolate mofetil \(MMF\)/mycophenolic acid \(MPA\)](#). 22 January 2018
- [Mycophenolate mofetil, mycophenolic acid: new pregnancy-prevention advice for women and men](#). Drug Safety Update. December 2015

Article citation: Drug Safety Update volume 11 issue 7; February 2018: 2.

Gadolinium-containing contrast agents: Omniscan and iv Magnevist no longer authorised, MultiHance and Primovist for use only in liver imaging

A recent Drug Safety Update article in December 2017 advised that the licences for gadodiamide (Omniscan) and intravenous gadopentetic acid (also known as gadopentetate dimeglumine; Magnevist) will be suspended from 1 February 2018.

Omniscan and intravenous Magnevist are now no longer authorised for use and a product recall of any existing unexpired stock is underway (see [Class 2 Medicines Recall](#)).

The linear agents gadobenamic acid (also known as gadobenate dimeglumine; MultiHance) and gadoxetic acid (Primovist) should now only be used for liver imaging and when imaging in the delayed phase is required.

Macrocyclic agents gadoteridol (Prohance), gadobutrol (Gadovist), and gadoteric acid (Dotarem) remain authorised, as does gadopentetic acid for intra-articular use only. For further information see [December 2017 Drug Safety Update](#).

Article citation: Drug Safety Update volume 11 issue 7; February 2018: 3.

Letters sent to healthcare professionals in January 2018

In January 2018, an update was sent to healthcare professionals about [a defect with the antiepileptic drug Buccolam \(midazolam\)](#) and a risk of inhalation/ingestion of tip cap of prefilled plastic syringes (see [press release from MHRA](#)).

Pharmacists are encouraged to proactively communicate the [instructions](#) included in this letter to parents and caregivers (and patients if appropriate) who have been dispensed Buccolam and who have not already been made aware. Further supplies of Buccolam will contain these instructions, which are to be provided with every pack dispensed.

In addition, in January 2018 the following letters were sent to relevant healthcare professionals:

- Misoprostol vaginal delivery system (Mysodelle): [Reports of excessive uterine tachysystole \(contractions\) that may not respond to tocolytic treatment](#)
- Noradrenaline (Norepinephrine) 0.08 mg/mL (4 mg in 50 mL) solution for infusion in a vial: [potential risk of medication errors](#)
- Relenza (zanamivir): supply of Taiwanese stock; [give patients UK leaflet](#)
- Mycophenolate mofetil (MMF)/mycophenolic acid (MPA): [amended recommendations for contraception in male patients](#)

We are also aware of the following two letters, sent to relevant healthcare professionals in December 2017:

- Flolan (epoprostenol sodium) and [leakage of administration sets containing PETG](#)
- Fludara 10 mg film-coated tablets: [Polish language blisters](#)

Article citation: Drug Safety Update volume 11 issue 7; February 2018: 4.

Medical Device Alerts issued in January 2018

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see [Alerts and recalls for drugs and medical devices](#).

Alerts were recently issued by MHRA about:

- [All Philips HeartStart MRx monitors/defibrillators – significant delay in the supply of batteries](#)
- [Pacemakers and CRT-P, manufactured by Boston Scientific - oversensing of minute ventilation sensor signal leading to risk of syncope and pre-syncope](#)

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