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Direct Healthcare Professional Communication
Mycophenolate mofetil (MMF)/mycophenolic acid (MPA): amended recommendations for contraception

Dear Healthcare Professional,

The Marketing Authorisation holders, in agreement with the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

Male patients - new advice

- The 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.
- Male patients of reproductive potential should be made aware of the potential risks of fathering a child. As a precautionary measure for male patients, it is recommended that the patients **or** their female partner use reliable contraception during treatment and for at least 90 days after stopping mycophenolate medicines.

  Male patients planning to have children should be advised to discuss the implications of both immunosuppression and any prescribed medications on pregnancy with their doctor.

Female patients – reminder

- The risk for women is unchanged. Mycophenolate medicines remain contraindicated in women of child bearing 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.
- For female patients of child bearing potential, **at least one reliable form of contraception** must be used before, during and for 6 weeks after stopping mycophenolate medicines. Two forms of contraception are preferred but not mandatory.

Background on the safety concern

Mycophenolate, used to prevent transplant rejection, is a major human teratogen known to cause miscarriages and congenital malformation when used in pregnant women. Between 45% and 49% of cases of exposure to mycophenolate in the womb result in miscarriage, and between 23% and 27% result in malformations.

Mycophenolate medicines – both mycophenolate mofetil (MMF)[1] or mycophenolic acid (MPA)– are therefore contraindicated in women of child bearing potential not using effective contraception. Mycophenolate is also contraindicated in pregnant women unless there are no suitable alternatives to prevent transplant rejection. In addition, negative pregnancy tests are required before starting treatment (as described in the product information for these medicines).

[1] MMF is a pro-drug of MPA

Following a recent in-depth review of non-clinical and clinical data regarding men fathering children while being treated with MMF and MPA, the European Medicines Agency (EMA) has updated its 2015 recommendations for MMF and MPA to prevent pregnancy.

Although the amount of mycophenolate present in semen has not been determined, calculations based on animal data show that the maximum amount of mycophenolate that could potentially be transferred to a woman is low and is unlikely to have any effect. However, mycophenolate has been shown to be genotoxic in animal studies at concentrations higher than the human therapeutic exposure levels, and the risk of genotoxic effects on sperm cells can therefore not be completely excluded. The available clinical evidence while reassuring is currently insufficient to determine the risks in humans, however this is being continually monitored.

The previous recommendation that male patients should use condoms in addition to their female partners using a highly effective contraception has now been removed from the product information. The recommendation is now that as a precaution sexually active male patients **or** their female partners should use contraception during treatment and for at least 90 days after stopping mycophenolate.

The risks for women are unchanged. Women of childbearing potential must use **at least one form of reliable contraception** before starting, during, and for 6 weeks after stopping treatment with mycophenolate unless abstinence is the chosen method of contraception. However, two complementary forms of contraception are preferred to minimise the risk of contraception failure.

Call for reporting

Please continue to report suspected adverse drug reactions (ADR's) to the MHRA through the Yellow Card Scheme. Please report all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

It is easiest and quickest to report ADRs online via the Yellow Cards website - https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- or by downloading and printing a form

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact points

Alternatively, suspected adverse reactions may also be reported to the Marketing Authorisation holders or their authorised distributor using the details provided below. If you have further questions or require additional information, please contact:

Company	Product name	Email	Phone	Fax
Accord Healthcare Limited	Mycophenolate mofetil capsules, film coated tablets and 500mg powder for concentrate for solution for infusion Mycophenolic acid 180 mg and 360	Additional Information: Medinfo@accord-healthcare.com Suspected adverse reactions: Medinfo@accord-	Additional Information: +44 (0)1271 385 257 Suspected adverse reactions:+44 (0)1271	N/A

	mg gastro-resistant tablets	healthcare.com	385 257	
Actavis UK Limited	Mycophenolate mofetil 250mg capsules and 500mg tablets	Additional Information: Medinfo@accord-healthcare.com Suspected adverse reactions: Medinfo@accord-healthcare.com	Additional Information: +44 (0)1271 385 257 Suspected adverse reactions: +44 (0)1271 385 257	N/A
Ascend Laboratories (UK) Limited	Mycophenolate mofetil 250 mg capsules and 500 mg film-coated tablets	Additional Information: ujwal.chhabra@alkem.com Suspected adverse reactions: pvglobal@alkem.com	Additional Information: +91 22 2741 2731 Suspected adverse reactions: +44 7712 559700	+91 22 2741 2547
Generics (UK) Limited t/a Mylan	Mycophenolate mofetil 500 mg film-coated tablets	Additional Information: info.uk@mylan.co.uk Suspected adverse reactions: info.uk@mylan.co.uk	Additional Information: 01707 853000 (choose Option 1) Suspected adverse reactions: 01707 853000 (choose Option 6)	N/A
Morningside Healthcare Limited	Mycophenolate mofetil 500 mg film-coated tablets	Additional Information: medicalenquiry@morningsidehealthcare.com Suspected adverse reactions: morningsidepvg@apcpharma.co.uk	Additional Information: 01162045950 Suspected adverse reactions: 0208 326 3220	0116 24707 56
Novartis Pharmaceuticals UK Limited	Myfortic 180mg and 360mg gastro-resistant tablets	Additional Information: email: medinfo.uk@novartis.com Suspected adverse reactions: email: uk.patientsafety@novartis.com online: through patient safety information (PSI) tool at https://psi.novartis.com	Additional Information: 01276 698370	N/A
Roche Products Limited	CellCept 250mg capsules, 500mg film coated tablets, 500mg powder for concentrate for solution for infusion and 1g/5ml powder for oral suspension	Additional Information: medinfo.uk@roche.com Suspected adverse reactions: welwyn.uk_dsc@roche.com	Additional Information: +44 (0)800 328 1629 Suspected adverse reactions: +44(0)1707 367554	N/A
Rowex Ltd and members of the	Mycophenolate mofetil Sandoz 250 mg capsules, hard and 500 mg film-	Additional Information: sandoz@professionalinformati	Additional Information and	N/A

Sandoz group including Sandoz Ltd	coated tablets Mycophenolate Sandoz 250 mg capsules Mycophenolate Hexal 250 mg capsules Mycophenolate mofetil Hexal 500 mg film-coated tablets Mycophenolate Lek 250 mg capsules Mycophenolate mofetil Lek 500 mg film-coated tablets Mycophenolate 1A Pharma 250 mg capsules Mycophenolate mofetil 1A Pharma 500 mg film-coated tablets Mycot 250 mg Capsules and 500 mg film-coated tablets Ceptava 180 mg and 360 mg gastro-resistant tablets	on.co.uk Suspected adverse reactions: https://psi.novartis.com	Suspected adverse reactions: +44 (0) 12766 98020	
Teva UK Limited	Myfenax 500mg film coated tablets and 250mg hard capsules Mycophenolate mofetil 500mg tablets and 250mg capsules	Additional Information: medinfo@tevauk.com Suspected adverse reactions: uk.safety@tevauk.com	Additional Information: +44 (0) 207 540 7117 Suspected adverse reactions: +44 (0) 207 540 7337	+44 (0) 207 540 7349
Wockhardt UK Limited	Mycophenolate mofetil 500mg film-coated tablets	Additional Information: Drug.safety@wockhardt.co.uk Suspected adverse reactions: Drug.safety@wockhardt.co.uk	Additional Information: +44 (0)1978 669 272 Suspected adverse reactions: +44 (0)1978 669 272	N/A

Annexes Prescribing Information for mycophenolate mofetil and mycophenolic acid is available either via The European Medicines Agency website at http://www.ema.europa.eu/ema/ , via the MHRA website at http://www.mhra.gov.uk/spc-pil/ or via the Electronic Medicines Compendium at http://www.medicines.org.uk/emc and this will be updated.

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