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EMA recommends additional measures to prevent use of mycophenolate in pregnancy

Pregnant women must not be exposed unless there is no suitable alternative to prevent transplant rejection

The European Medicines Agency (EMA) has warned that the transplant medicine mycophenolate (authorised centrally as CellCept and nationally under various names) must not be used in pregnancy unless no suitable alternative is available to prevent transplant rejection. This follows a routine re-assessment of the benefits and safety of these medicines, which provided updated evidence on the risk of birth defects and spontaneous abortions when pregnant women were exposed to the medicine.

Although the product information for these medicines already contains warnings against use in pregnancy, these will now be significantly strengthened by the addition of new contraindications, advice and information. Updated product information will emphasise that women and men using the medicine should use effective contraception and that pregnancy tests should be used before and during treatment as needed to rule out unintended pregnancy. In addition, doctors should properly explain the risks to patients and their partners, and educational material will be produced for patients and healthcare professionals to assist with this.

Information for patients

- Mycophenolate medicines are intended for patients who have had an organ transplant. They help prevent the body rejecting the transplanted organ by suppressing the immune system.
- If a pregnant woman is exposed to mycophenolate, either by taking it herself or through unprotected sex with a man taking the medicine, it is likely to harm the developing baby. About half of all pregnancies in women taking the medicine end in miscarriage, and around a quarter of surviving babies are born with birth defects.
- Mycophenolate must therefore not be used in women who are pregnant or might become pregnant unless there is no suitable alternative treatment to prevent transplant rejection.
- Before starting the medicine, women who could become pregnant should undergo pregnancy testing. One test about 8 to 10 days before starting and another immediately before starting treatment are recommended. Pregnancy tests should be repeated if necessary during treatment (for example, if contraception is missed).



- Women who are able to become pregnant should use two reliable methods of contraception simultaneously during treatment with mycophenolate, and for 6 weeks after stopping.
- Sexually active men taking mycophenolate are recommended to use condoms during sex and to continue doing so for at least 90 days after stopping treatment; their female partners should also use effective contraception during the same period.
- Patients taking mycophenolate should also not donate blood during treatment or for 6 weeks afterwards, and men should not donate sperm during treatment or for 90 days after stopping.
- Patients should not stop taking the medicine without advice. If women think they may have become pregnant during treatment they must consult their doctor immediately.
- Patients will be provided with information and counselling on the possible risks if mycophenolate is used during pregnancy. Patients who have any concerns should consult a healthcare professional.

Information for healthcare professionals

- Mycophenolate (mycophenolate mofetil or mycophenolic acid) is a confirmed teratogen associated with an increased rate of spontaneous abortion and congenital malformation compared with other immunosuppressants.
- It must not be used during pregnancy unless there is no suitable alternative to prevent transplant rejection. Pregnancy should be ruled out by use of a sensitive serum or urine test; one test 8 to 10 days before starting mycophenolate and another immediately before starting the medicine is recommended.
- Mycophenolate should not be used in women of childbearing potential unless they are using highly effective contraception. Women should use two reliable methods of contraception simultaneously before starting and during therapy, and for 6 weeks after stopping treatment.
- Sexually active (including vasectomised) men taking mycophenolate are recommended to use condoms for sex during treatment and for 90 days thereafter; partners of childbearing potential are also recommended to use highly effective contraception for the same period.
- Patients should be advised not to donate blood during or for 6 weeks after stopping treatment, and men should not donate sperm during therapy or for 90 days after stopping.
- Patients should be counselled to make sure they understand the risks and the measures required to minimise them. They should be advised not to stop mycophenolate without speaking to a healthcare professional, and to consult immediately if they believe they may have become pregnant.
- A 'Dear Healthcare Professional' letter and educational materials from the company about the teratogenic risk and giving advice on contraception and pregnancy testing will be provided.

EMA's recommendations are based on the assessment of updated evidence on the teratogenic risks.

- A cumulative review found that around 45 to 49% of pregnancies in women exposed to mycophenolate resulted in spontaneous abortion, compared with reported frequencies of 12 to 33% in solid organ transplant patients treated with other immunosuppressants.
- The reported incidence of malformation in the offspring of mothers exposed to mycophenolate during pregnancy is 23 to 27% compared with 4 to 5% in transplant patients treated with other immunosuppressants, and 2 to 3% in the overall population. Malformations associated with

mycophenolate have included abnormalities of the ear, eye and face, congenital heart disease including septal defects, polydactyly or syndactyly, tracheo-oesophageal malformations such as oesophageal atresia, effects on the nervous system such as spina bifida, and renal abnormalities.

More about the medicine

Mycophenolate (mycophenolate mofetil or mycophenolic acid) is an immunosuppressant (a medicine that suppresses the action of the immune system, the body's natural defences). It is approved for use with other medicines to prevent rejection of the transplanted organ in patients given a kidney, heart or liver transplant. In the EU, mycophenolate mofetil has been authorised centrally as CellCept and other names since 1996, and mycophenolate has also been authorised through various national procedures.

More about the procedure

This update of the product information follows a regular re-assessment of the benefit-risk balance of the medicine known as a 'periodic safety update review' or 'PSUR', carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines. All medicines approved in the EU undergo such re-assessments at defined periods, to ensure that their balance of benefits and risks remains favourable.

Following its review the PRAC recommended changes to the product information, which were sent to the Committee for Medicinal Products for Human Use (CHMP), which is responsible for questions concerning medicines for human use. The CHMP approved the changes for CellCept in the context of a procedure called a 'type II variation'. The CHMP opinion will now be forwarded to the European Commission, which will issue a legally binding decision applicable in all EU Member States. Further action will be taken at a national level to align the product information for other mycophenolate products.

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