Date: 03 December 2018

Direct Health Care Professional Communication

Subject: Teratogenicity in association with mycophenolate mofetil

Dear Healthcare professional,

Hikma Pharmaceuticals would like to inform you that exposure to Myora® (mycophenolate mofetil) during pregnancy is associated with an increased risk of first trimester pregnancy loss and congenital malformations.

Summary:
The objective is to improve patient understanding and reduce the number of unplanned pregnancies to women taking mycophenolate by having a conversation between the HCP and the patient.

The following should be discussed with female patients of reproductive potential:
• The increased risks of first trimester pregnancy loss and congenital malformations while taking mycophenolate.
• Pregnancy tests should be conducted before and during mycophenolate treatment.
• Birth control needs to be used while taking mycophenolate, and for 6 weeks after stopping treatment, to avoid pregnancy.
• Pregnancy planning needs to be discussed with a healthcare provider if a patient wishes to become pregnant during mycophenolate treatment.
• All pregnancies need to be reported.

This information is being sent in agreement with the SFDA.

SFDA will continue to monitor safety information associated with the use of those products as it does for all medicinal products on the Local market, to identify and assess potential harms, and will keep Healthcare providers updated.

Further information on the safety concern and the recommendations:
Teratogenic effects
Mycophenolate is a powerful human teratogen. Spontaneous abortion (rate of 45-49%) and congenital malformations (estimated rate of 23-27%) have been reported following MMF exposure during pregnancy. Therefore, Mycophenolic acid is contraindicated in pregnancy unless there are no suitable alternative treatments to prevent transplant rejection. Female and male patients of reproductive potential should be made aware of the risks (e.g. contraceptive methods, pregnancy testing) prior to, during, and after therapy with Mycophenolic acid.

Congenital malformations, including reports of multiple malformations, have been observed post-marketing in children of patients exposed to Mycophenolic acid during pregnancy in combination with other immunosuppressants. The following malformations were most frequently reported:
- Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear), external auditory canal artesia;
- Congenital heart disease such as atrial and ventricular septal defects;
- Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;
- Abnormalities of the eye (e.g. coloboma);
- Malformations of the fingers (e.g. polydactyly, syndactyly);
- Tracheo-Oesophageal malformations (e.g. oesophageal atresia);
- Nervous system malformations such as spina bifida;
- Renal abnormalities.

In addition, there have been isolated reports of the following malformations:
- Microphthalmia;
- congenital choroid plexus cyst;
- septum pellucidum agenesis;
- olfactory nerve agenesis. Studies in animals have shown reproductive toxicity.

Physicians should ensure that women and men taking mycophenolate understand the risk of harm to the baby, the need for effective contraception, and the need to immediately consult their physician if there is a possibility of pregnancy.

Contraception
Because of the genotoxic and teratogenic potential of Mycophenolic acid, women with childbearing potential should use two reliable forms of contraception simultaneously before starting Mycophenolic acid therapy, during therapy, and for six weeks after stopping the therapy; unless abstinence is the chosen method of contraception.

Sexually active men are recommended to use condoms during treatment and for at least 90 days after cessation of treatment. Condom use applies for both reproductively competent and vasectomised men, because the risks associated with the transfer of seminal fluid also apply to men who have had a vasectomy. In addition, female partners of male patients treated with Mycophenolic acid are recommended to use highly effective contraception during treatment and for a total of 90 days after the last dose of Mycophenolic acid.

Before starting Mycophenolic acid treatment, women of child bearing potential should have a pregnancy test in order to exclude unintended exposure of the embryo to mycophenolate. Two serum or urine pregnancy tests with a sensitivity of at least 25 mIU/mL are recommended; the second test should be performed 8 – 10 days after the first one and immediately before starting Mycophenolic acid. Pregnancy tests should be repeated as clinically required (e.g. after any gap in contraception is reported. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should pregnancy occur.

Mycophenolate is a powerful human teratogen, with an increased risk of spontaneous abortions and congenital malformations in case of exposure during pregnancy;

- Spontaneous abortions have been reported in 45 to 49% of pregnant women exposed to Mycophenolic acid, compared to a reported rate of between 12 and 33% in solid organ transplant patients treated with immunosuppressants other than Mycophenolic acid.
- Based on literature reports, malformations occurred in 23 to 27% of live births in women exposed to Mycophenolic acid during pregnancy (compared to 2 to 3 % of live births in the overall population and approximately 4 to 5% of live births in solid organ transplant recipients treated with immunosuppressants other than Mycophenolic acid).

Further information:

Mycophenolate Mofetil (Myora®) is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

Call for reporting:

Healthcare professionals are encouraged to report any adverse reactions or other safety information related to mentioned medications to the SFDA.

Postal address:

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Annexes

1. Mycophenolate mofetil – prescriber guide. Last accessed: 22-Nov-18. Available from: https://www.medicines.org.uk/emc/rmm/393/Document
2. Anderka, MT. Lin, AE. Abuelo, DN. Et al. Reviewing the evidence for mycophenolate mofetil as a new teratogen: case report and review of the literature. Am J Med Genet A. 2009 Jun; 149A(6): 1241-8.
3. Coscia, A. Armenti, DP. King, RW. Et al. Update on the tertaogenecity of maternal mycophenolate mofetil. J pediatr Genet. 2015 Jun; 4(2): 42-55.

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