Biro Pengawalan Farmaseutikal Kebangsaan
National Pharmaceutical Control Bureau
KEMENTERIAN KESIHATAN MALAYSIA
MINISTRY OF HEALTH MALAYSIA

Ruj. Kami: (37) dlm. BPFK/PPP/07/25
Tarikh : 25 MAR 2016

SEMUA PEMEGANG PENDAFTARAN

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/ Puan,

PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984
ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 6 TAHUN 2016: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI MYCOPHENOLATE (MYCOPHENOLATE MOFETIL DAN MYCOPHENOLIC ACID): PENGEMASKINIAN SISIP BUNGKUSAN DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN TERATOGENIK

Adalah saya merujuk kepada Arahan Bilangan 6 Tahun 2016 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 6 Tahun 2016 telah bersetuju untuk pengemaskinian sisip bungkusan dengan maklumat keselamatan berkaitan risiko kesan teratogenik bagi semua produk yang mengandungi mycophenolate (mycophenolate mofetil dan mycophenolic acid) seperti pada surat arahan Bil. (37) BPFK/PPP/07/25.

3. Pihak pemegang pendaftaran adalah diarahkan untuk mematuhi keperluan tersebut.

Sekian, terima kasih.

"**BERKHIDMAT UNTUK NEGARA**"

Saya yang menurut perintah,

(TAN ANN LING)
Pengarah Regulatori Farmasi
Biro Pengawalan Farmaseutikal Kebangsaan
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BPFK/PPP/07/25 (37)

ARAHAN DI BAWAH PERATURAN 29 PERATURAN – PERATURAN KAWALAN DADAH DAN KOSMETIK 1984

BILANGAN 6 TAHUN 2016

DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI MYCOPHENOLATE (MYCOPHENOLATE MOFETIL DAN MYCOPHENOLIC ACID): PENGEMASKINIAN SISIP BUNGKUSAN DENGAN MAKLUMAT KESELAMATAN BERKAITAN RISIKO KESAN TERATOGENIK

TUJUAN

1.1 Arahan ini dikeluarkan oleh Pengarah Kanan Perkhidmatan Farmasi di bawah Peraturan 29 (1) Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984.

1.2 Arahan ini ditujukan kepada semua pemegang pendaftaran semua produk yang mengandungi mycophenolate (mycophenolate mofetil dan mycophenolic acid) bagi mengemaskini sisip bungkusan dengan maklumat keselamatan berkaitan risiko kesan teratogenik.

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **298** pada **11 Mac 2016** telah membuat keputusan bagi semua produk yang mengandungi mycophenolate (mycophenolate mofetil dan mycophenolic acid) untuk mengemaskini sisip bungkusan dengan maklumat keselamatan berkaitan risiko kesan teratogenik.

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi mycophenolate (mycophenolate mofetil dan mycophenolic acid) seperti berikut:-

3.1.1 Pada bahagian ***Contraindications***

.....

- *[Product name] is contraindicated during pregnancy due to its mutagenic and teratogenic potential (see Use in Special Populations: Pregnancy).*
- *[Product name] is contraindicated in women of childbearing potential not using highly effective contraceptive methods (see Use in Special Populations: Pregnancy).*
- *[Product name] is contraindicated in women who are breastfeeding (see Use in Special Populations: Breastfeeding).*

3.1.2 Pada bahagian ***Use in Special Populations***

Pregnancy

[Product name] is contraindicated during pregnancy and in women of childbearing potential not using highly effective contraceptive methods. (see Contraindications).

Before the start of treatment, female and male patients of reproductive potential must be made aware of the increased risk of pregnancy loss and congenital malformations and must be counseled regarding pregnancy prevention, and planning.

Prior to starting therapy with [product name], female patients of childbearing potential must have ***two negative serum or urine pregnancy tests*** *with a sensitivity of at least 25 mIU/mL; The second test should be performed 8-10 days after the first one and immediately before starting [product name]. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. Patients should be instructed to consult their physician immediately should they become pregnant.*

Due to the mutagenic and teratogenic potential of mycophenolate, ***women of child bearing potential*** *should use* ***two reliable forms of contraception*** *simultaneously, including at least one highly effective method, before beginning mycophenolate therapy, during therapy, and for six weeks following discontinuation of 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*** *are recommended to*

use highly effective contraception during treatment and for total of 90 days after the last dose of [product name].

Congenital malformations, including multiple malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy. The following malformations were most frequently reported:

- *Facial malformations such as cleft lip, cleft palate, micrognathia and hypertelorism of the orbits;*
- *Abnormalities of the ear (e.g. abnormally formed or absent external/middle ear) and eye (e.g. coloboma, microphthalmos);*
- *Malformations of the fingers (e.g. polydactyly, syndactyly, brachydactyly);*
- *Cardiac abnormalities such as atrial and ventricular septal defects;*
- *Oesophageal malformations (e.g. oesophageal atresia);*
- *Nervous system malformations (such as spina bifida).*

In the medical literature, malformations in children from mycophenolate-exposed pregnancies have been reported in 23% to 27% of live births. For comparison, the risk of malformations is estimated at approximately 2% of live births in the overall population and at approximately 4% to 5 % in solid organ transplant patients treated with immunosuppressants other than mycophenolate.

Cases of spontaneous abortions have also been reported in patients exposed to mycophenolate, mainly in the first trimester. In the medical literature, the risk has been reported at 45% to 49% following mycophenolate exposure, compared to a reported rate between 12 and 33% in solid organ transplant patients treated with other immunosuppressants.

Studies in animals have shown reproductive toxicity.

Breastfeeding

[Product name] is contraindicated during breastfeeding due to the potential for serious adverse reactions in nursing infants (see Contraindications).

Studies in rats have shown mycophenolate to be excreted in milk. It is not known whether this medicine is excreted in human milk.

3.1.3 Pada bahagian ***Adverse Drug Reactions***

Post-marketing experience:

Congenital Disorders

Congenital malformations have been reported post-marketing in children of patients exposed to mycophenolate in combination with other immunosuppressants during pregnancy (see Use in Pregnancy).

Pregnancy, Puerperium and Perinatal Conditions

Cases of spontaneous abortions mainly in the first trimester in patients exposed to mycophenolate have been reported (see Use in Pregnancy).

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada sisip bungkusan semua produk yang mengandungi mycophenolate (mycophenolate mofetil dan mycophenolic acid) bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 Jun 2016**

(b) Produk berdaftar : **1 Disember 2016**

5. Permohonan pindaan pada sisip bungkusan bagi produk berdaftar perlu dikemukakan sebagai permohonan variasi.

6. Tarikh kuat kuasa arahan ini ialah mulai **1 Jun 2016.**

"BERKHIDMAT UNTUK NEGARA"

(DATO' EISAH BINTI A RAHMAN)
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia
ra/nb/ppp/bpfk/160316

s.k. 1. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

2. Pengarah Amalan dan Perkembangan Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

3. Pengarah Regulatori Farmasi
Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia.