INCREASING ACCESS TO MIFEPRISTONE: PAVING THE PATH FOR REGISTRATION AND COMMERCIALIZATION FOR ADDITIONAL INDICATIONS

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RHSC Webinar
Register mifepristone for additional indications

– In countries that have no registered product, an alternative indication may bypass hurdles
– In countries with limited markets, additional indications may increase demand
– In countries where mife is underused, may reduce stigma and provide an entry point to being stocked at facilities
# of countries with mifepristone increasing; in places with restrictive abortion laws, access remains challenging

Persistent commodity gap in restrictive climates due to multiple barriers: registration, distribution, commercialization, demand creation – innovative market strategies needed!

Four clinical indications of interest: all are legal in most settings; meaning drug registration would not pose the same problems as most existing labeled products (1st tri abortion)

*It is possible:* Mifegyne® is already labeled for other reproductive health indications
**INDICATIONS**

- Treatment of early pregnancy loss
- Treatment of intra-uterine fetal death
- Second trimester abortion
- Cervical preparation prior to surgical abortion
- Uterine fibroids
- Emergency contraception
- Cushing’s disease
- Refractory depression
- Chemical dependence
- Labor induction at term

Different tablet size/dose
Different tablet size/dose; emerging evidence base
INDICATIONS AND USAGE

**MIFEPREX** is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.

**Mifegyne: 4.1 Therapeutic indications**

1. **Medical termination of developing intra-uterine pregnancy.**
   In sequential use with a prostaglandin analogue up to 63 days of amenorrhea.

2. **Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.**

3. **Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons** *(beyond the first trimester).*

4. **Labour induction in foetal death in utero**
   in patients where prostaglandin or oxytocin cannot be used.
Interviews conducted with: MSI, PSI, Danco, Linepharma, Naari, IPPF, DKT, Concept Foundation

- High interest in exploring labeling other indications for mifepristone
- Mixed knowledge of available evidence
- Different understandings as to requirements to add a labeled indication
- No consensus on most promising indication
- Insufficient time (human resources) & money to pursue
GLOBAL ASSESSMENT: INDICATIONS

❖ What indications are most widely known?
  – Incomplete abortion, missed abortion, second trimester abortion, IUFD
  – Some interest in labeling a product for menstrual regulation

❖ Which are considered most promising?
  – No consensus: incomplete abortion, cervical ripening, second trimester abortion, IUFD
  – One respondent mentioned that it would be helpful to have a stand-alone mife product for new indication
    • Product could be registered for another indication and used in combination with existing/available misoprostol products at country-level
**Global Assessment: Challenges & Priorities**

- **Why do it?**
  - Political barriers making access to formal registration and availability of these products for induced abortion difficult
  - Small market, hard to interest local distributors in politically sensitive use, manufacturers currently don’t view mifepristone as a profitable product

- **Where should efforts focus?**
  - Where donors support us
  - In West Africa
  - In South America
COUNTRY-LEVEL ASSESSMENTS

❖ **Why?** To assess interest in mifepristone for other indications and to gather perspectives on what might be a viable indication moving forward.

❖ **Where?** 6 countries, regional representation, including places where 1) no mifepristone product currently registered for any indication, 2) limited legal abortion status, 3) known interest in exploring mifepristone registration for indications other than 1st tri abortion.

❖ **Countries selected:** Burkina Faso, Colombia, Kenya, Latvia, Pakistan, Senegal

❖ **Who?** Key stakeholders including staff from Ministries of Health or drugs and regulatory bodies, health care providers and national staff of international NGOs
**Context:** Abortion is not permitted by law. It is completely banned by the criminal code, although permitted to save a woman’s life by the medical code. Abortion is highly stigmatized including within medical profession, although it is widely performed. No real efforts to register mifepristone. Misoprostol is registered and used widely both to prevent and treat PPH and for PAC. It is widely known that medications available in pharmacies are used for abortions.

**Potential benefit:** agreement that “alternative” indications would be good. Legal registration of a mife product or combi-pack will provide “cover” for all involved, regardless of legal status.

**Which indication:** no consensus on which indication might be most useful. Multiple indications are more likely to result in availability and use of mifepristone. The indication should be “non-abortion related” so as to not cause controversy.

**Challenges:** highly controversial topic. No one wants to talk about abortion openly. Registering a product for an indication that is not legal is considered risky.
BURKINA FASO

- **Context:** Abortion is legally restricted and highly socially stigmatized. Abortion is legal in cases where it is necessary to save the mother’s life, in cases of rape or incest and severe fetal malformation. New provisions in law make performing abortions easier. It is widely understood that abortion is provided but not discussed. Two combi-pack products are currently registered in Burkina Faso but not available in public sector (included on EML).

- **Potential benefit:** New indications may help reduce backlash if they are medical (medically necessary) in nature. First trimester abortion is not perceived as medically necessary.

- **Which indication:** There was no agreement on a most useful new indication however, it should be one that causes the “least disruption” (could be 2nd tri.) To garner more support, a new indication should focus on “saving mother’s lives” or be placed globally in the context of reproductive health (non-abortion).

- **Challenges:** The social and political environment has posed a challenge for widespread marketing and distribution of mifepristone for first trimester abortion. Mifepristone is not registered for other indications. Attempts to change label will place more attention on a potentially volatile topic area.
Context: Law allows abortions when mothers life is at risk. There are currently three combi-pack products registered. Available and used in country since 2013. Mifepristone and misoprostol are listed separately on country-level EML. Not provided in public sector but readily available in private sector. Drugs are not sold to women directly.

Potential benefit: Informants generally did not perceive a potential benefit for registering mife for other indications. However, additional indications may make it easier to use and potentially increase access in public sector. A new label could also serve as “training” for providers to ensure proper use for various indications.

Challenges: Potential for backlash since use is currently larger than allowed indications “Is changing the label worth the potential backlash?”
Context: Abortion is available by law in cases where it is needed to save a woman’s life or as a necessary health treatment. Misoprostol is registered in Pakistan for both PAC and PPH, and there is a locally manufactured product that is available and of high quality. It is widely used by providers as an abortifacient, although it is not registered for first trimester abortion.

Potential benefit: Agreement that additional indications would be good; could destigmatize the product and increase access; having mife available for other indications would constitute a clinical improvement and offer choice over miso used alone (e.g. increase effectiveness, fewer side effects)

Which indication: Pregnancy failure (missed abortion or IUFD)

Challenges: Misoprostol is widely available and cheap; so a mife product would need to be affordable
Context: Abortion is legally available on demand until 12 weeks. MA legal until 7 wks GA; mifepristone and misoprostol both registered for 1\textsuperscript{st} tri abortion > 9 wks GA; MA provided almost exclusively through the private sector, and service delivery volume is low.

Potential benefit: Informants did not perceive a potential benefit for registering mifepristone for other indications in Latvia

Why? Mifepristone is technically available and off-label drug use is reported to be commonplace

To increase access to mifepristone, informants suggested:
1) greater availability, including in the public sector,
2) lower the cost,
3) provider education, particularly on alternative indications, and
4) revision of the law to permit MA ≥ 9 wks GA.
Context: In 2006, the constitutional court ruled that abortion should be available in cases of rape or incest, to save or preserve a woman’s health or where the fetus has a malformation incompatible with life. Since then, national guidelines have included mifepristone as an option for abortion through 10 weeks’ pregnancy (2014) and mandate that all facilities provide abortion (2018), at least by referral. Despite the guidelines, in practice, medical abortion is still almost exclusively available in the private sector. While the 2017 mife registration limits use to 70 days but recent guidelines (RIA) allow for use in the second trimester.

Potential benefit: Responses favored broadening mife registration for other indications

Which indication? Second trimester abortion (cervical priming and missed abortion also considered feasible)

Challenges: Lack of awareness that mife is available in Colombia – even among providers; concern from some (not all) about rocking the boat given the current administration; funding
# In Sum

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Interest</th>
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<tbody>
<tr>
<td>Burkina Faso</td>
<td>YES</td>
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<td>Senegal</td>
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<td>Colombia</td>
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<td>Kenya</td>
<td>MAYBE</td>
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<td>Pakistan</td>
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<tr>
<td>Latvia</td>
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Conclusions

– Mixed knowledge of available evidence and/or requirements to add a labeled indication

– No consensus on most promising indication across countries but some consensus w/in countries

– Alternative indications are viable; parallel strategies needed to increase the # of registrations and to better understand market sustainability
Next Steps

- Convene strategy meeting/s to gain consensus on who, what and how to register mifepristone for alternative indications.
  - **Global level**, to define & align strategy among global stakeholders & to ensure collaboration & rational use of resources. (Maybe RHSC can be convening body?)
  - **At the country level**, to define strategy and identify champions who can provide advocacy and support buy-in for successful registration. (Countries with clear interest: Burkina Faso, Senegal, Colombia)

- Ensure parallel strategies / activities to develop provider capacity, revise or introduce national practice guidelines, determine where & how drug will be made available & collaborate in-country & within-country on mife procurement.

- Incorporate market stabilization strategies into strategies for registration.
- Convene webinar to improve knowledge and understanding of mifepristone registration, marketing, distribution and availability.
Advocacy Messaging

Mifepristone’s multiple RH indications: An overlooked opportunity for expanding access

When evidence supports safe and effective use of a medication or device, women should be given a choice of options for their care, and this applies to treatments involving mifepristone. Often mifepristone represents a non-invasive treatment alternative which may make it especially attractive to health systems as well as to women.

Mifepristone is a progestin which blocks the activity of the hormone progesterone which is needed to maintain a pregnancy. Mifepristone also plays a role in softening and dilating the cervix and can be used to achieve cervical priming for medical procedures. It is most commonly known for its use in combination with the drug misoprostol to induce a medical abortion.

Although the number of countries with access to mifepristone grows every year, the medication is still not available in many places. In others, it is officially registered but unobtainable due to a variety of stigma and market-related barriers. As a result, populations that could benefit, including women and girls, the young and disenfranchised, rural and remote populations, are not able to access this safe, effective medication.

Evidence Summary by Indication

Early Pregnancy Loss

EXPLANATION OF INDICATION
Early pregnancy loss occurs in 15-20% of all recognized pregnancies. One type of early pregnancy loss is a “missed abortion” wherein a non-viable pregnancy is retained. This includes spontaneous abortions and cases of embryonic or early fetal demise. Treatment may be sought to expel the pregnancy and, in many cases, this involves expectant management or other health care staff or may be induced with misoprostol. Using medications for uterine evacuation in an armamentarium allows for an effective and safe alternative. Research on the use of mifepristone for miscarriage has recently advanced.

SUMMARY OF EVIDENCE
Some early studies included mifepristone, with or without misoprostol, for management of missed abortion with mixed results. These studies highlighted issues around consistent use definitions. A large randomized-controlled trial published in the New England Journal of Medicine reports that pretreatment with mifepristone prior to misoprostol for management of early pregnancy loss resulted in complete evacuation in significantly more participants compared to misoprostol alone and a recently completed randomized-controlled trial on missed abortion showed that pretreatment with mifepristone results in fewer miscarriages. The current evidence supports the same regimen of mifepristone and misoprostol contained in a package. The large ongoing trial in the UK on this topic: https://www.medicinenet.com/mifepтрат/
REFERENCES


# Briefing Document

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendations in International Guidelines</th>
<th>Existing products with this indication in label?</th>
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<tbody>
<tr>
<td>Early Pregnancy Loss</td>
<td><strong>NICE</strong>: Do not offer mifepristone as a treatment for missed or incomplete miscarriage. (Ectopic Pregnancy and Miscarriage: diagnosis and initial management NG128, 2012) <strong>WHO</strong>: Misoprostol is the recommended treatment for incomplete abortion and inevitable abortion and there is no mention of mifepristone for early pregnancy loss in the guidelines. (Medical Management of Abortion 2018; Management of Complications of Pregnancy and Childbirth 2017)</td>
<td>No</td>
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<td>IUFD</td>
<td><strong>WHO</strong>: Medical management of IUFD includes the use of mifepristone in combination with misoprostol (recommended) or misoprostol alone (alternate). (Medical Management of Abortion 2018) <strong>RCOG</strong>: a combination of mifepristone and a prostaglandin preparation is recommended as the first-line treatment for late intrauterine death and stillbirth for women with unscarred uteruses. For women with a history of lower segment cesarean sections, mifepristone can be used alone. (Greentop Guidelines 55, 2010) <strong>NICE</strong>: if a woman who has had a late IUFD chooses to proceed with induction of labour, mifepristone should be used, followed by vaginal prostaglandin E2 or misoprostol. (NICE clinical guideline 70, 2013)</td>
<td><strong>Mifeprine</strong>® (Exelenva, France): Labour induction in foetal death in utero. In patients where prostaglandin or oxytocin cannot be used. <strong>Mediprist</strong>® (Acme, India): To induce labour in cases where the foetus has died in the womb and where it is not possible to use other medical treatments (prostaglandin or oxytocin).</td>
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<td>2nd Trimester medical abortion</td>
<td><strong>WHO</strong>: For medical management of induced abortion ≥12 weeks gestation...We suggest the use of 200 mg mifepristone administered orally, followed 1–2 days later by repeat doses of 400 μg misoprostol administered vaginally, sublingually or buccally every 3 hours. (Medical Management of Abortion 2018) <strong>FIGO</strong>: &gt;13 weeks. If mifepristone is available (preferable), follow the regimen prescribed for mifepristone + misoprostol. 200 mg mifepristone followed 36-48 hours later by repeat doses of 400 μg misoprostol or bucc. There is no maximum dose of misoprostol recommended. <strong>RCOG</strong>: Medical abortion regimens using 200 mg oral mifepristone and misoprostol are effective and appropriate at any gestation. (Clinical Guideline #7, 2011)</td>
<td><strong>Mifeprine</strong>® (Exelenva, France): Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons (beyond the first trimester). <strong>Mediprist</strong>® (Acme, India): As pre-treatment before giving prostaglandins for termination of pregnancy for medical reasons beyond 3 months gestation.</td>
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Thank yous

- Briefing document and project report available – please contact Gynuity and RHSC
- Paul Blumenthal, Hillary Bracken, Nathalie Kapp for reviewing the briefing document
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- All those who participated in the interviews
- RHSC for supporting this work
ANY QUESTIONS?