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Original Research Article

A cross-sectional analysis of mifepristone, misoprostol, and combination mifepristone-misoprostol package inserts obtained in 20 countries ☆,☆☆

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ABSTRACT

Objectives: To evaluate the characteristics, clinical information, and storage instructions contained in package inserts from medical abortion commodities collected in low- and middle-income countries.
Study design: From November 2017 to February 2018 mifepristone, misoprostol, and combined mifepristone-misoprostol (combipack) products were collected to populate the Medical Abortion Commodities Database. We extracted stated indications for use, storage instructions, and date of last revision from each package insert obtained. For those inserts listing medical abortion as an indication, we also extracted eligibility criteria, recommended regimens, side effects, and contraindications.
Results: We identified 41 package inserts from 20 countries; 19 (46%) listed medical abortion as an indication including all 7 combipacks, all 7 mifepristone products, and 5/27 (19%) misoprostol products. Date of last insert revision ranged from 1991 to 2016. Gestational age limits for early medical abortion ranged from 49 days to "first trimester." Three (43%) mifepristone products recommended a 600 mg oral dose and two (29%) recommended regimens with gemeprost. Eighteen (67%) misoprostol and one (14%) combipack inserts recommended protection from moisture.
Conclusions: The characteristics, clinical information, and storage instructions in medical abortion product package inserts from a variety of field settings in low- and middle-income countries included inadequate storage instructions and outdated gestational age limits and regimens.
Implications: There is an urgent need to revisit approved inserts for medical abortion products in low- and middle-income countries to ensure information is accurate and reflects the current evidence base. Simultaneously, providing supplemental instructions targeted at users may fill some gaps. People have a right to accurate information to ensure a safe and effective medical abortion experience.

1. Introduction

The purpose of a medication package insert is to provide complete and unbiased prescribing and safety information to health professionals [1]. Requirements for the content of these inserts differ by country, but the United States Federal Drug Authority (FDA) requires information including indication and usage, dosage and administration, contraindications, warnings and precautions, adverse reactions, and drug interactions [2]. Typically the package insert is a document generated during the regulatory process and is approved by country-level regulatory authorities. Updates or changes generally require initiative and expense on the part of manufacturers or distributors. In some situations the prescribing information, intended for a 'learned intermediary,' is supplemented by a patient package insert.

Medical abortion pills include mifepristone, misoprostol, and combined mifepristone-misoprostol (combipack) products. Misoprostol, an off-patent drug with multiple indications, is often available in pharmacies. In select settings, mifepristone (also off-patent) and combipacks are also available. Illegal and black market sales of these medications abound [3–5]. Depending on location, people have access to these drugs within and sometimes outside the formal health system. In the case of informal acquisition of these drugs the package insert may be the only piece of information available to end-users.

There is growing interest in self-managed abortion and how it changes the reproductive health field. Package inserts may play

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an amplified role in the case of self-managed abortion because providers may not be the primary source of information. A group of abortion researchers identified a research gap regarding the distribution and provision of medical abortion information and drugs at a 2016 conference [6].

There are many acceptable regimens for medical abortion with misoprostol and it can be used alone or in combination with mifepristone [7–13]. The initial medical abortion protocol involved mifepristone 600 mg but large clinical trials demonstrated that a one-pill regimen of mifepristone 200 mg was equally effective [14]. The 2019 WHO recommendations for induced medical abortion under 12 weeks gestation include the use of mifepristone 200 mg oral followed by misoprostol 800 mcg buccally, vaginally, or sublingually. Alternatively, a misoprostol-alone regimen using repeated doses of 800 mcg buccally, vaginally, or sublingually can be used [15].

In November 2017, the International Planned Parenthood Federation (IPPF), in partnership with Gynuity Health Projects and Concept Foundation, began creating an inventory of medical abortion products available around the world. This data collection effort resulted in a rich dataset of package inserts available to end-users of these medications. We performed an analysis of 41 unique package inserts collected as of February 2018 to explore their characteristics, clinical information, and storage instructions.

2. Materials and methods

We analyzed data collected for the initial population of the Medical Abortion Commodities Database using methods fully described at www.medab.org. Briefly, data collectors obtained all available mifepristone, misoprostol, or combipacks products from at least five different outlets (including public and private hospitals, pharmacies, drug shops) in at least two cities in countries identified by IPPF as high priority and scanned the box and package insert. For this analysis we used the inserts found in the drug boxes obtained at sites.

Researchers first evaluated the completeness and readability of physical copies or scanned images of each insert. We excluded documents missing a page or with poor-image quality and limited abstraction to inserts in English, French, Spanish, and Portuguese.

We considered inserts "unique" if they were not collected in the same country as other inserts with identical product names, manufacturers, and insert dates. While some products were sold as "combipacks", if they consisted of a bundled pack of mifepristone and misoprostol but had no combination packaging or insert, we considered them separate products.

Researchers fluent in the written language extracted product characteristics (brand name, commodity type, country of collection), the stated indications for use, the storage instructions, the date of last revision, the manufacturer, and identified whether the insert provided prescriber information and/or patient specific instructions. We recorded information about storage instructions from the inserts themselves, even if instructions on the boxes differed.

For each product specifically labeled for medical abortion, we abstracted clinical information including eligibility criteria, recommended regimens, precautions, and contraindications.

We used Microsoft Excel for our database and present the data using descriptive statistics. Illustrative quotations from inserts were extracted manually.

3. Results

3.1. Description of sample

We obtained a total of 138 inserts and excluded 29 for readability (poor quality [n = 26], missing page [n = 3]), 47 for language (Cyrillic script [n = 32], Vietnamese [n = 15]), and 21 duplicates, leaving 41 unique inserts (27 misoprostol, 7 mifepristone, 7 combipacks) for analysis. The dataset included inserts from 20 countries (Burkina Faso, Côte D'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Indonesia, Mali, Mexico, Moldova, Mozambique, Myanmar, Niger, Senegal, South Africa, Tanzania, Tunisia, Uganda, Uruguay, Vietnam, and Zambia). Among the 41 unique package inserts were 23 brand names and 20 manufacturers. Only 15/41 (37%) inserts recorded the date of last revision and those dates ranged from 1991 to 2016. Most inserts contained information on indication, eligibility, regimen, side effects, precautions, storage, and manufacturer. While most inserts mentioned the medication was a pill and listed the number of pills contained in the box, only about half (21/41) described the appearance of the pills (e.g. white and round) (Table 1).

All mifepristone and combipack products were labeled for early medical abortion. Two of seven mifepristone inserts also included cervical preparation prior to surgical termination of pregnancy, labor induction for intra-uterine fetal death, and pre-treatment for second trimester medical abortion as additional indications. The misoprostol inserts varied widely in terms of which indications were listed, including gastric ulcer, postpartum hemorrhage, post abortion care, cervical ripening, treatment of intrauterine fetal death, labor induction, and medical abortion. The most common indication listed was related to gastric ulcer (22/27 (81%)) which is the originator indication for the drug. Many misoprostol product inserts listed multiple indications for use, but none listed all evidence-based indications (Table 2).

3.2. Storage

All but three of the 41 inserts contained storage information although the content of this information varied. Another three inserts expressly stated there were no particular storage requirements. While we did not have the boxes for every product, among those we had (n = 23) six had different storage instructions on the box and insert. All combipacks (7/7) and the majority of mifepristone (5/7) and misoprostol (23/27) inserts mentioned protecting the product from heat with recommended maximum temperatures of 25 or 30 degrees Celsius. The majority (18/27, 67%) of misoprostol inserts recommended protection from moisture but only 14% of combipacks inserts (1/7), which contain misoprostol, included this instruction (Table 3).

3.3. Medical abortion-labeled products

Of the 41 unique products abstracted, 19 included medical abortion as an indication on the insert (7 mifepristone, 5 misoprostol and 7 combipacks).

Table 1
Components present on unique package inserts for medical abortion commodities collected in low- and middle-income countries N = 41.

Components of Inserts	n (%)
Indication	40 (98)
Eligibility	40 (98)
Regimen (any indication)	39 (95)
Side effects	41 (100)
Precautions	41 (100)
Storage	38 (93)
Manufacturer	38 (93)
Date of insert revision	15 (37)
Appearance	21 (51)

Table 2
Indications listed on misoprostol product package inserts collected in low- and middle-income countries $n = 27$.

Date of last revision	Indication					
	Medical Abortion	Postpartum Hemorrhage	Post Abortion Care	Gastric Ulcer	Cervical Ripening	Intrauterine Fetal Death
Missing	Yes	No	Yes	Yes	No	No*
Missing	Yes	Yes	No	Yes	Yes	Yes
Missing	Yes	No	No	Yes	No	No
Missing	Yes	No	No	Yes	No	No
Missing	Yes	No	No	No	No	No
Missing	No	Yes	Yes	Yes	Yes	Yes
Missing	No	Yes	Yes	Yes	Yes	Yes
Missing	No	Yes	Yes	Yes	Yes	Yes
Missing	No	Yes	Yes	Yes	Yes	Yes
Missing	No	Yes	Yes	Yes	Yes	Yes
Apr-14	No	Yes	Yes	No	No	No
Nov-16	No	Yes	Yes	No	No	No
Sep-12	No	Yes	Yes	No	No	No
Missing	No	Yes	Yes	No	No	No
Jul-11	No	No	No	Yes	No	No
Nov-13	No	No	No	Yes	No	No
Jul-11	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
Nov-11	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
Jan-91	No	No	No	Yes	No	No
Mar-14	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
Nov-10	No	No	No	Yes	No	No
Missing	No	No	No	Yes	No	No
TOTAL *n* (%)	5 (19)	10 (37)	10 (37)	22 (81)	6 (22)	5(22)

* Also labor induction.

Table 3
Storage instructions on package inserts*** for medical abortion product collected in low- and middle-income countries $N = 41$.

	Mifepristone $n = 7$	Misoprostol $n = 27$	Combipack* $n = 7$
Protect from heat	5 (71)	23 (85)	7 (100)
Protect from moisture	2 (29)	18 (67)	1 (14)
Protect from light	2 (29)**	4 (15)	2 (29)
State no particular conservation necessary	1 (14)	2 (7)	0 (0)
No storage instructions mentioned	1 (14)	2 (7)	0 (0)

* Combipacks consist of co-packaged misoprostol and mifepristone products.
** One insert that said "ensure box is well closed" was included in the "protect from light" category.
*** One mifepristone insert and one misoprostol insert had no storage instructions but the product boxes did; additionally one combipack and two misoprostol inserts listed only protection from heat but the product boxes also mentioned moisture; one misoprostol insert mentioned heat and moisture but the box only mentioned heat. Information from product boxes is not included in the table above.

Some of these inserts contained inconsistencies with regard to the indication listed and the content of the clinical information. For example, two combipacks labeled exclusively for medical abortion contained a warning of the risk of meconium passage and caesarean delivery which seems to apply to misoprostol use in labor induction.

Additionally some misoprostol product inserts indicated that the drug should not be used in pregnant women while at the same time giving instructions for use as an abortifacient. This reflects the haphazard combination of various recommendations and perhaps an absence of formal scientific review.

3.4. Use of language

Roughly one-third (6/19) of medical abortion inserts were directed at the end user, using language like "tell your doctor if…" and 3 of the 6 were set up in a question and answer format. These fit the description of a patient package insert. The remaining inserts (13/19, 68%) were more clearly prescriber information, using language like "If a patient…" and containing more technical information e.g. pharmacokinetics.

Over 70% (14/19) of the medical abortion inserts analyzed were written in English, four of which contained an additional language (Vietnamese or Russian). The remaining inserts were written in Spanish ($n = 3$), French ($n = 1$), or Portuguese ($n = 1$) (Table 4).

Some of the inserts were clearly translated from another language and contained errors. These errors ranged from awkward wording such as "for patients of young age type diabetes" to actual inaccuracies such as "grapefruit juice" translated to "*jugo de uva*" [grape juice], and even some mistranslations that could affect treatment course, including the following incomplete thought and confusing explanation "*Dos días después de la prostaglandina se administra Usted debe quedarse y descansar durante 3 horas después de la prostaglandina*" [Two days after administering the prostaglandin you should stay and rest for 3 h after the prostaglandin.]

3.5. Eligibility criteria

The gestational age limit for early medical abortion eligibility varied across the 19 inserts. Three of 19 inserts (16%) did not list a gestational age limit and another 4 listed an upper limit of 49 days, reflecting the originator product label. The remaining inserts listed 56 or 63 days or simply "first trimester" with none mentioning 70 days. Three mifepristone inserts listed both a first trimester gestational age limit (56 days; 63 days; and 63 days) as well as an indication for later use ("beyond the first trimester" "beyond 3 months" "between 13 and 20 weeks").

Inconsistency in how inserts used the terms eligibility, contraindication, warning, and precaution complicated direct comparison of eligibility criteria. Broadly, 100% of the mifepristone or

Table 4
Characteristics of inserts of products labeled for medical abortion collected in low- and middle-income countries n = 19.

	n (%)[***]
Product	
Misoprostol	5 (26)
Mifepristone	7 (37)
Combipacks[*]	7 (37)
Type of Insert	
Provider information	13 (68)
Patient information	6 (32)
Language	
English	14[**] (74)
Spanish	3 (16)
French	1 (5)
Portuguese	1 (5)
Gestational age limit	
None listed	3 (16)
≤49 days	4 (21)
≤56 days[****]	1 (5)
≤63 days[****]	9 (47)
≤70 days	0 (0)
"First trimester"	2 (11)

[*] Combipacks consist of co-packaged misoprostol and mifepristone products.
[**] Four of the English inserts also had another language on the back, 3 Vietnamese 1 Moldovan.
[***] Percentages may not add to 100 due to rounding.
[****] Three inserts (1 with a limit of ≤56 days; 2 with ≤63 days) also included an indication beyond the first trimester.

combipack inserts mentioned suspected ectopic pregnancy, inherited porphyria, and allergy to mifepristone as contraindications. Additionally, the majority of mifepristone and combipack inserts mentioned some form of the following contraindications: unconfirmed pregnancy, chronic adrenal failure, hemorrhagic disorders, allergy to misoprostol or prostaglandin, long-term corticosteroid therapy, anticoagulant therapy, and limited access to care for emergency treatment. Misoprostol inserts were less consistent in their lists of contraindications.

Other contraindications listed on at least one insert included: cardiovascular disease, renal failure, severe uncontrolled asthma (mifepristone, misoprostol, and combipack); hepatic impairment (mifepristone and combipack); severe anemia, previous cesarean section, age < 18 years (combipack); age < 16 years (misoprostol); and age > 35 years and smoking > 10 cigarettes a day (mifepristone).

3.6. Medical abortion drug regimens

In this sample, 20 regimens were recommended on 19 products labeled for medical abortion (two mifepristone products and one combipack had two regimens, two misoprostol products lacked a regimen). The majority of regimens that included mifepristone (13/17, 77%) recommend using 200 mg of that drug. All these regimens recommended the mifepristone pills be taken by the oral route. All mifepristone labels recommended use in combination with a prostaglandin to cause medical abortion: the recommended prostaglandin was either misoprostol (5/9, 56%), gemeprost (2/9, 22%), or unspecified (2/9, 22%). Doses of misoprostol for medical abortion with mifepristone ranged from 400 mcg to 800 mcg and routes included oral, vaginal, and unspecified. Some inserts had different regimens based on gestational age. For example, one recommended mifepristone 600 mg and misoprostol 400 mcg for pregnancies up to 49 days but gemeprost (a vaginal pessary that needs to be kept frozen) [16] as the prostaglandin for pregnancies between 50 and 63 days.

Among combipacks the regimens were more consistent with all 7 inserts recommending mifepristone 200 mg oral and misoprostol 800 mcg. Four combipack inserts mentioned an additional dose of misoprostol 400 mcg for gestations >49 days if the first dose did not produce bleeding within four hours. Routes of misoprostol administration varied with some inserts providing options.

Misoprostol products labeled for medical abortion included one that offered a misoprostol-alone regimen using repeated doses of 800 mcg administered sublingually, buccally, or vaginally; two that had no regimen information for medical abortion but included regimen information for gastric ulcer; and two that had incomplete information regarding the mifepristone portion of the regimen (Table 5).

3.7. Medical abortion failure

Inserts differed on the instructions for how to handle method failures. Instructions ranged from suggesting that the pregnancy can be continued, to providing prenatal care instructions if a pregnancy is continued, to insisting that an alternative termination method be used.

[If a woman wants to continue with a pregnancy that has been exposed, it is not necessary to require completion.]

"in the case this method does fail, it is a must to use another method to terminate the pregnancy"

[In case of a pregnancy termination failure… if you decide to continue the pregnancy, close prenatal care and repeated ultrasounds… should be undertaken at a specialized center]

4. Discussion

This analysis of information contained in medical abortion product packages obtained during a global exercise to populate the Medical Abortion Commodities Database revealed significant variations in the information available in the packages. While off-label use of medications, particularly misoprostol, for medical abortion is common, this analysis focused on products labeled for that indication as a starting point.

The dates on the inserts are suggestive of the accuracy and relevance of the information presented. As new science around drug regimens, eligibility, and storage requirements emerges, inserts must be updated accordingly. The oldest dated insert was from 1991 which meant its recommendations predated much of the current scientific knowledge. The evidence-based gestational age cutoff for outpatient medical abortion has incrementally advanced over time; The initial medical abortion protocols stopped at 49 days [17], a cutoff stated on nearly a quarter of inserts, which has the potential to exclude a wide swath of people for whom these drugs may be safe and effective. In 2016, the USFDA approved an updated label for Mifeprex (Danco) which extended the gestational age limit to 70 days [18].

The 2019 WHO recommendations use mifepristone 200 mg [15] and while this dose was recommended in the majority of inserts, the persistence of the older 600 mg dose on some suggests inefficiencies and a possible unnecessary cost. The differing regimens by gestational age are also dated and may reflect the incremental addition of information, instead of an ongoing process of reviewing and re-writing inserts when evidence changes.

As many advances have been made to medical abortion protocols there has been a corresponding decrease in safety concerns around their use. Side effects that pertained to older regimens may now be alleviated, contraindications that were once of concern may now have been shown to be safe [7]. The long and varied list of contraindications suggests that these portions of the documents may represent accretion by default with insufficient revi-

Table 5
Medical abortion regimens listed on product inserts collected in low- and middle-income countries $n = 20$.

Product	Date of last insert revision	GA limit (days)	Mifepristone regimen		Recommended prostaglandin	Prostaglandin interval (hours)***	Prostaglandin	
			Dose	Route			Dose	Route
Mifepristone	May 2008******	56	600 mg	oral	unspecified	36–48	unspecified	oral
	Sep 2012	49	600 mg	oral	misoprostol	48	400 mcg	oral
	missing**,******	63	200 mg	oral	misoprostol	36–48	400 mcg	oral
		63	200 mg	oral	gemeprost	36–48	1 mg	vaginal
	missing	63	200 mg	oral	unspecified	48	unspecified	unspecified
	Dec 2015**, ******	49	600 mg	oral	misoprostol	36–48	400 mcg	oral
		63	600 mg	oral	gemeprost	36–48	1 mg	vaginal
	missing	49	200 mg	oral	misoprostol	48	400 mcg	unspecified
	missing	49	200 mg	oral	misoprostol	48	400 mcg	unspecified
Combipack*	missing	63	200 mg	oral		24–72	800 mcg	Vaginal****
	missing	63	200 mg	oral		24–72	800 mcg	vaginal****
	missing	63	200 mg	oral		36–48	800 mcg	vaginal
	missing	63	200 mg	oral		24–48	800 mcg	vaginal or sublingual
	Apr 2016	63	200 mg	oral		24–72	800 mcg	vaginal****
	Nov 2016	63	200 mg	oral		24–72	800 mcg	oral and vaginal****
	missing**	<63	200 mg	oral		24–48	800 mcg	buccal/sublingual or vaginal
		>63	200 mg	oral		36–48	800 mcg	buccal/sublingual or vaginal
Misoprostol	missing*****	First Trimester	n/a	n/a		n/a	800 mcg q 3–4 h max 3	sublingual or buccal or vaginal
	missing	missing	missing	missing		48	400 mcg	oral
	missing	missing	missing	missing		48	400 mcg	oral

* Combipacks consist of co-packaged misoprostol and mifepristone products.
** Insert provided two regimens.
*** If inserts said 1–2 days, tabulated as 24–48 h; 1–3 days as 24–72.
**** These regimens allowed for additional misoprostol 400 mcg orally or vaginally if the gestational age was 49–63 days and no bleeding occurred after 4 h.
***** This insert pertains to a misoprostol-alone regimen.
****** In addition to the first trimester regimen presented, these inserts also had information on mifepristone use outside of the first trimester but did not include the type, dose, or route for the prostaglandin GA = Gestational age.

sion when safety evidence mounts or regimens change. The documents may represent more of a clearinghouse of one-time concerns instead of a current list of evidence-based contraindications. Clinical guideline differences likely reflect different regulatory processes for approval. However, these elements of the package inserts, if adhered to, have the potential to unnecessarily restrict the pool of eligible users.

The lack of storage information for some products may have implications for drug quality. While mifepristone is quite stable [19], misoprostol can degrade when exposed to moisture, particularly if not in ideal packaging (double-sided aluminum blisters) [20,21].

In our sample, the information on misoprostol inserts was less complete and accurate than that found on mifepristone and combipacks. While misoprostol's multiple indications provide numerous avenues for availability, including in restrictive settings, this feature may also pose difficulty for end users relying on package inserts to provide information for medical abortion.

The mix of inserts addressed to providers and to patients confirms the suspicion that these inserts are not exclusively for prescriber information, suggesting that there may be a role for supplements to standard inserts in some contexts.

We did not purposefully design data collection with the aim to evaluate the content of inserts but rather leveraged an existing dataset to explore possible issues. Medical Abortion Commodities database partners pre-selected countries for data collection for the primary purpose of the development of the database, so the absence of certain countries or regions has no intrinsic meaning. Additionally, analysis was limited to inserts in English, Spanish, French, and Portuguese. Data collection was not exhaustive in each country, and existing products may be missing from the dataset; poor quality images resulted in the exclusion of some inserts that may have been informative. As products were obtained from points of sale, it is possible that some were fraudulent and others imported outside of the formal regulatory process. Thus some of the inserts may not have been subject to regulatory approval. Some of the inserts may also be older versions that have since been updated.

This study suggests that there is variation in the information provided on package inserts for medical abortion commodities in low- and middle-income countries and that there is a need to ensure that accurate, complete, and up-to-date information is distributed. Such dissemination could result from country-level regulatory authorities revisiting the package inserts approved in their jurisdictions, from manufacturers updating the inserts on their products, or from non-government actors providing supplemental information to users. People seeking medical abortion should have the information they need for a safe and effective experience.

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