

# MISOPROSTOL

TABLETS, 200 MICROGRAMS

## GENERAL PRODUCT INFORMATION

Misoprostol is a synthetic analog of a natural prostaglandin E1. It has been widely approved for treatment and prevention of peptic ulcer disease for over a decade before it was investigated as a uterotonic and oxytocic agent. As a result, misoprostol is currently used for two distinct purposes:

- Gastroprotection and healing of peptic and duodenal ulcers
- A variety of obstetric and gynecological indications, including medical abortion, medical management of miscarriage, induction of labor, cervical ripening before surgical procedures, and prevention and treatment of PPH

Misoprostol is considered an essential medicine by the UN Commission on Life-Saving Commodities for its PPH indication because PPH is the leading cause of maternal death. This document therefore focuses on misoprostol for its use in PPH only.

The WHO's Essential Medicine List (EML) recommends using misoprostol for preventing and treating PPH when oxytocin is unavailable or cannot be administered safely. Although oxytocin injection is the recommended medicine for the prevention and treatment of PPH, the limitations of oxytocin are that it requires a cold chain and skilled administration to deliver effective results. These two conditions cannot always be met in low-resource settings. Misoprostol does not need cold chain storage and its simple tablet form facilitates its use by community health workers and traditional birth attendants. The drug's ease of use and stability at room temperature make it suitable for delivery in low-resource settings. It is therefore recommended as an alternative to oxytocin in the prevention and treatment of PPH where oxytocin use is not feasible or safe.

Furthermore, the WHO recent guideline recommends advance misoprostol distribution to pregnant women for self-administration for prevention of PPH in settings where women give birth outside of

a health facility and in the absence of skilled health personnel, provided that appropriate monitoring and evaluation is implemented.<sup>1</sup>

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<sup>1</sup> WHO. 2020. "WHO recommendation on advance misoprostol distribution to pregnant women for prevention of postpartum hemorrhage." Geneva: WHO. Available at <https://apps.who.int/iris/bitstream/handle/10665/336310/9789240013902-eng.pdf?sequence=1&isAllowed=y>

## KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO, approved by an SRA, or recommended by the ERP and with a proven record of quality products.
2. The procurer must obtain evidence of the quality, and in particular, the stability of the product from the manufacturer before ordering as the use of inappropriate excipients or inadequately controlled environmental conditions can increase exposure to moisture and cause product degradation. Pre-shipment testing is pointless for inappropriately manufactured and packaged product—the product may comply with specifications shortly after manufacturing but may only have 50 percent of labeled content within six months.

## KEY QUALITY CONSIDERATIONS

### **Product specification**

Misoprostol finished product must comply with the quality specifications as detailed in “[Product Specifications](#)” section below.

### **Packaging and labeling**

The packaging requirement for misoprostol is double-aluminum blister packs. Packaging is critical for the stability of misoprostol; double-aluminum blister packs effectively protect the products from moisture and prevent degradation.

Products presented in PVC or PVDC/aluminum blister packs should never be purchased because PVC or PVDC/aluminum do not provide adequate protection against penetration by moisture.

When procuring SRA-approved products, the suitability of packaging for the intended markets should be reassessed. For example, some misoprostol products approved in SRA markets (climatic zone II) are packaged in plastic bottles, which is not suitable for use in countries in climatic zones III and IV with high temperature and humidity.

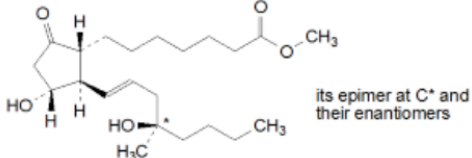
Procurers should ensure that package inserts of the products eligible for procurement include information on the PPH indications and dosages. This is particularly important because the dose for PPH prevention (400-600 micrograms) and treatment (800 micrograms) are significantly higher than the dose for induction which is 25 micrograms. The most common presentation of misoprostol is a 200 mcg. tablet which cannot be safely broken to create a 25 mcg. dose. For induction, a 25 mcg. tablet should be procured or a 200 mcg tablet dissolved in sterile water and titrated to oral dose. Misoprostol has a variety of obstetric and gynecological indications, including PPH. However, only a few products are registered for those indications. Many misoprostol products are registered for gastric ulcer uses and manufacturers’ package inserts do not provide information specific for the PPH indication.

Additional information about the packaging and labeling can be found in the Annex.

### Storage, transportation, and distribution

Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablet form.

Additional information about the misoprostol finished product storage requirement can be found in the “[Storage, Stability and Degradation](#)” section below.

<b>Name of the Medicinal Product</b>	Misoprostol
<b>Chemical Name</b>	(±) methyl 11 $\alpha$ , 16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate.
<b>Chemical Structure</b>	<p>C<sub>22</sub>H<sub>38</sub>O<sub>5</sub></p>  <p>its epimer at C* and their enantiomers</p>
<b>Pharmaceutical Form</b>	For use in the prevention and treatment of PPH, misoprostol is available in an oral tablet form, which can be administered orally or sublingually.
<b>Qualitative and Quantitative Composition</b>	<p>Each tablet contains 200 micrograms (mcg) of misoprostol.</p> <p>List of typical excipients<sup>2</sup>:</p> <ul style="list-style-type: none"> <li>– Microcrystalline cellulose</li> <li>– Hydrogenated castor oil</li> <li>– Sodium starch glycolate</li> <li>– Hypromellose</li> </ul>
<b>Packaging and Presentation</b>	Typically, cold-form double-aluminum blister (Alu/Alu) is used for primary packaging. Secondary packaging is normally suitable cardboard to protect from damage.

## SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA and/or recommended by the Expert Review Panel are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from trusted sources, such as manufacturers

<sup>2</sup> Based on the formulation of an innovator product, Cytotec®.

approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in [Module II](#).

### WHO-prequalified products

As of June 2022, three misoprostol 200 mcg tablets are prequalified by the WHO PQP, as shown below. It is recommended to check the updated information at the time of procurement, which can be found at: <https://extranet.who.int/pqweb/content/prequalified-lists/medicines>

Table M-1. List of WHO Prequalified Misoprostol Tablets

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH039	Cipla Ltd, Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai, Maharashtra, 400 013, India	FPP manufacturing site: Cipla Ltd, Unit 8, Plot No. L-139, S-103 and M-62, Verna Industrial Estate, Salcette, Goa, 403 722, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 4x1, 4x7, 4x15	8-Apr-14	2 years	Do not store above 30°C.
RH048*	China Resources Zizhu Pharmaceutical Co Ltd, No 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China	FPP manufacturing site: China Resources Zizhu Pharmaceutical Co Ltd, No. 27 Chaoyang North Road, Chaoyang District, Beijing, 100024, China API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 3x1, 4x1	22-Nov-16	2 years	Do not store above 30°C.
RH056*	Acme Formulation Pvt. Limited, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India	FPP manufacturing site: Acme Formulation Pvt. Ltd, Hormone Block, Ropar Road, Nalagarh, Distt. Solan, Himachal Pradesh, 174101, India API manufacturing site: (misoprostol dispersion (1:100 in HPMC)) Piramal Healthcare UK Ltd, Whalton Road, Morpeth, Northumberland, NE61 3YA, UK	Misoprostol tablet 200 mcg	Blister Alu/Alu: 10x10	27-Apr-16	2 years	Do not store above 30°C; protect from light.

\* Include the indication for PPH.

## SRA-approved products

Table M-2. Examples of SRA-Approved Misoprostol 200 mcg Tablets

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Cytotec 200 mcg tablets*	UK MHRA	Pfizer Limited	PL 00057/0956	Oral tablet; cold-formed aluminum blister pack	3 years	Do not store above 30°C. Store in the original package to protect from moisture.
Cytotec*	US FDA	Pfizer	NDA #019268	Oral tablet; bottle	Not specified	Store at or below 25°C, in a dry area.
Misoprostol*	US FDA	Novel Labs Inc.	ANDA #091667	Oral tablet; bottle	Not specified	Store at 20–25°C. [See USP controlled room temperature.] Store in a dry area.
GyMiso 200 mcg, comprimé**	ANSM, France	Linepharma, France	34009 362 499 4 3	Oral tablet; blister pack (Paper/PE/Aluminum)	2 years	Store at a temperature not exceeding 25°C
Cytotec tablets (misoprostol 200 mcg)*	Swissmedic	Pfizer <b>AG</b>	46945	Oral tablets; not specified	Not specified	Store at room temperature (15-25°C).
Cytotec misoprostol 200 mcg tablet blister pack*	TGA Australia	Pfizer Australia Pty Ltd	AUST R 63983	Oral tablet; cold formed Alu/Alu blister pack	3 years	Store below 25°C; protect from moisture.
Cytotec misoprostol 200 mcg tablet bottle—EX (export only)*	TGA Australia	Pfizer Australia Pty Ltd	AUST R 46849	Oral tablet; bottle	3 years	Store below 30°C
GyMiso misoprostol 200 mcg oral tablet blister pack***	TGA Australia	MS Health Pty Ltd	AUST R 188015	Oral tablet; Alu/Alu blister pack	2 years	Store below 25°C in the original packaging.

\* Registration for gastrointestinal indications.

\*\* Registration for the indications of medical interruption of intrauterine pregnancy, in combination with mifepristone; and preparation of the cervix before surgical interruption of pregnancy during the first trimester.

\*\*\* Registration for the indication of medical termination of a developing intrauterine pregnancy, in sequential combination with mifepristone.

It should be noted that the list of SRA-approved products provided in the table above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- UK MHRA: <https://products.mhra.gov.uk/>
- EU regulatory authorities: [https://ec.europa.eu/health/documents/community-register/regca\\_en](https://ec.europa.eu/health/documents/community-register/regca_en)
- Swissmedic: Error! Hyperlink reference not valid. <https://www.swissmedicinfo.ch/>
- Health Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>.

## Related products

Other formulations of misoprostol that exist in the market include the following products:

<b>Vaginal tablet 25 mcg</b>	Included in the WHO EML, only for use for induction of labor where appropriate facilities are available.
<b>Misoprostol oral tablet 100 mcg</b>	Indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of complications from gastric ulcer; for example, the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer.
<b>Misoprostol oral tablet 400 mcg (e.g., Topogyne®, Misoone®)</b>	Indicated for medical termination of developing intrauterine pregnancy, in sequential use with mifepristone.
<b>Misoprostol vaginal 200 mcg vaginal delivery system (e.g., Mysodelle®, Misodel®)</b>	A controlled release formulation that releases misoprostol at a rate of approximately 7 micrograms/hour over a period of 24 hours  Indicated for induction of labor in women with an unfavorable cervix, from 36 weeks gestation, in whom induction is clinically indicated.



**Combination pack  
of mifepristone and  
misoprostol  
(e.g., Medabon®,  
MS-2 Step)**

Included in the WHO EML, only for use for medical abortion where permitted under national law and where culturally acceptable

Consists of 1 tablet of mifepristone 200 mg tablet and 4 tablets of misoprostol 200 mcg tablet

It is important to note that for the PPH indication the WHO EML recommends the use of misoprostol 200 mcg tablets for convenient use in accordance with the dosing regimens. WHO recommends 400 mcg or 600 mcg orally for the prevention of PPH,<sup>1</sup> and sublingual misoprostol at 800 mcg for controlling PPH<sup>2</sup> when oxytocin is unavailable (or its quality cannot be guaranteed) or skilled health personnel are not present to administer injectable uterotonics.

## STORAGE, STABILITY, AND DEGRADATION



Misoprostol tablets are stable at room temperature and do not require cold chain storage. However, exposure to water has been shown to be the principal driver in the degradation of misoprostol in tablets.

Misoprostol turns into three main inactive degradation products: type A, type B, and 8-epimer misoprostol. The inactive type A misoprostol occurs by dehydration, which produces water. The 8-epi misoprostol is obtained by isomerization. These degradation processes are catalyzed by the presence of water. The type B misoprostol is the result of isomerization of the inactive type A. The rate of degradation increases as water content increases.

It is therefore important to exclude water (moisture) at all stages of the manufacturing process and during storage of the product to ensure that the product will be stable throughout its shelf life. Critical factors related to exclusion of moisture include:

- Selection of API
- Selection of excipients
- Production environment (temperature and relative humidity)
- Packaging

Packaging is very important for the stability of misoprostol. A study of the quality of misoprostol sampled in the field<sup>3</sup> has shown that misoprostol tablets packaged in PVC-aluminum blisters are likely to degrade more rapidly than those packaged in aluminum-aluminum blisters, especially under conditions of high temperature and humidity.

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Therefore, misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.

<sup>1</sup> WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at <http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1>

<sup>2</sup> WHO. 2012. "WHO recommendations for the prevention and treatment of postpartum hemorrhage." Geneva: WHO. Available at [https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf)

<sup>3</sup> WHO. 2016. "Quality of Misoprostol Products." In: *WHO Drug Information*. Vol. 30, No. 1. Geneva: WHO. Available at <https://apps.who.int/iris/bitstream/handle/10665/331040/DI301-35-39-eng.pdf?sequence=1&isAllowed=y>

Shelf life: 2–3 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Tables M-1 and M-2, respectively.

## PRODUCT SPECIFICATIONS



The product must meet the International Pharmacopeia specifications,<sup>4</sup> or the equivalent thereof.

Table M-3. International Pharmacopeia Specifications for Misoprostol Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification* a) HPLC	The retention time of the principal peak in the chromatogram obtained from solution (1) corresponds to the retention time of the peak due to misoprostol in the chromatogram obtained from solution (2).	1.14.4 High-performance liquid chromatography
Identification* b) TLC	The principal spot obtained with solution (1) corresponds in position, appearance and intensity to that obtained with solution (2).	1.14.1 Thin-layer chromatography
Dissolution	The amount in solution is not less than (NLT) 80% (Q) of the amount declared on the label.	5.5 Dissolution test for solid oral dosage forms
Related substances**	In the chromatogram obtained with solution (1): <ul style="list-style-type: none"> <li>– The sum of the areas of any peak corresponding to impurity A, B, and E is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (3.0%).</li> <li>– The area of any peak corresponding to impurity C, when multiplied by a correction factor of 0.76, is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%).</li> <li>– The area of any peak corresponding to impurity D is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).</li> </ul>	1.14.4 High-performance liquid chromatography
Assay***	90.0–110.0%	1.14.4 High-performance liquid chromatography
Uniformity of content	Each single unit contains within $\pm 15\%$ of the average amount of the active ingredient. However, if one individual unit deviates by more than $\pm 15\%$ but is within $\pm 25\%$ of the average amount of the active ingredient, examine a further 20 units drawn from the same original sample as the first 10 units. The preparation under test complies only if the amount of active ingredient found in	5.1 Uniformity of content for single-dose preparations

<sup>4</sup> As of June 2022, there are no monographs of misoprostol tablets published in the US or British Pharmacopeia; please check for updated information.

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
	no more than one out of 30 units deviates by more than $\pm 15\%$ of the average amount. None deviates by more than $\pm 25\%$ of the average amount.	

\* Either test A or B may be applied.

\*\* Impurity A = 8-epi-misoprostol

Impurity B = 12-epi-misoprostol

Impurity C = misoprostol A

Impurity D = misoprostol B

Impurity E = Methyl rac-(13E,16RS)-11 $\alpha$ ,16-dihydroxy-16,18-dimethyl-9-oxo-20-norprosta-13,17-dien-1-oate (mixture of 4 stereoisomers)

\*\*\* It is acceptable to use the average of the 10 individual results obtained in the test for “uniformity of content.”



## PART I: CLINICAL PARTICULARS

### Therapeutic indications

Misoprostol is used for a variety of obstetric and gynecological indications:

- Prevention and treatment of PPH where oxytocin is not available or cannot be safely used.
- Management of incomplete abortion and miscarriage.
- First-trimester abortion: misoprostol in combination with mifepristone is indicated for the medical termination of intrauterine pregnancy. The duration of pregnancy for which the product is approved may be different in different countries.
- Cervical ripening: cervical ripening prior to uterine instrumentation; cervical ripening for induction of labor in case of a live fetus and intrauterine fetal death.

It is also indicated for gastroprotection and healing of peptic and duodenal ulcers.

### Posology, method, and duration of administration<sup>1,2</sup>

Table M-4. Misoprostol Dosage Based on Indication

INDICATION	DOSAGE	NOTES
PPH prevention	400 or 600 mcg orally single dose	– Included in the WHO EML. – Exclude second twin before administration.
PPH treatment	800 mcg sublingually single-dose	– Included in the WHO EML.
Incomplete abortion	<14 weeks: 600 mcg orally single-dose or 400 mcg sublingually single-dose  ≥14 weeks: 400 mcg sublingually, vaginally or buccally 3-hourly (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Included in the WHO EML.
Missed abortion (<14 weeks)	800 mcg vaginally, sublingually or buccally (repeated doses can be considered when needed to achieve success of the abortion process)	– Ideally used at least 24 hours after mifepristone 200 mg.

<sup>1</sup> WHO. 2018. "WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage." Geneva: WHO. Available at <http://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1&ua=1>

<sup>2</sup> WHO. 2022. "Abortion care guideline." Geneva: WHO. Available at <https://www.who.int/publications/i/item/9789240039483>

INDICATION	DOSAGE	NOTES
Induced abortion (<12 weeks )	800 mcg vaginally, sublingually or buccally (repeated doses can be considered when needed to achieve success of the abortion process)	– Ideally used 24–48 hours after mifepristone 200 mg.
Induced abortion (≥12 weeks)	400 mcg vaginally, sublingually or buccally 3-hourly (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Ideally used 24–48 hours after mifepristone 200 mg.
Intrauterine fetal demise (≥14 to ≤28 weeks)	400 mcg sublingually or vaginally every 4–6 hours (providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision)	– Ideally used 24–48 hours after mifepristone 200 mg.
Induction of labor (third trimester)	25 mcg vaginally 6-hourly or 25 mcg orally 2-hourly or 25 mcg dissolved in 200 mL water, 25 mL given hourly	– Included in the WHO EML. – Make sure to use the correct dosage—overdose can lead to complications. – Do not use in women with previous cesarean section.
Cervical ripening prior to instrumentation (first trimester)	400 mcg sublingually 1–2 hours before procedure or 400 mcg vaginally or buccally 2–3 hours before procedure	– Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, and hysteroscopy. – The sublingual route is more effective for misoprostol administration

## Contraindications

- Hypersensitivity to misoprostol or to any of the excipients in the product
- Known allergy to prostaglandins

### Contraindications in abortion setting

- Inherited porphyria
- Chronic or acute adrenal or hepatic failure
- Known or suspected ectopic pregnancy

## Special warnings and precautions for use

Caution is warranted in women with preexisting heart disease or cardiovascular risk factors, as cardiovascular events have been reported in association with misoprostol.

Caution and clinical judgment are required for women using corticosteroids long term, and for those who have bleeding disorders or severe anemia.

When misoprostol is used for induction of labor, the mother and her fetus should be closely monitored immediately after it is given.

When misoprostol is used for abortion, women should be advised to return for follow-up if they are experiencing signs of ongoing pregnancy.

Misoprostol should not be used in children below pubertal age.

This medicinal product contains hydrogenated castor oil. This may cause stomach upset and diarrhea.

## Interaction with other medicinal products and other forms of interaction

Interaction studies show that the pharmacokinetics of propranolol and diazepam are not influenced by concomitant administration of misoprostol.

Misoprostol does not change the pharmacokinetics of antipyrine, suggesting that it does not induce hepatic enzymes.

In a pivotal study performed with misoprostol, no adverse events that would suggest the existence of an interaction between misoprostol and oxytocin were reported in women exposed to prophylactic oxytocin (intramuscular or intravenous) prior to administration of misoprostol.

### Combination with nonsteroidal anti-inflammatory drugs

Theoretically, concomitant use with nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the efficacy of misoprostol. However, no clinically meaningful effect has been shown upon co-administration.

## Fertility, pregnancy and lactation

### Pregnancy

Misoprostol must not be used during intact pregnancy in the first trimester when the intent is to proceed, as a risk of fetal malformation cannot be excluded when misoprostol is administered during pregnancy.

In a few cases where misoprostol was self-administered (orally or vaginally) during early pregnancy, the following deleterious effects have been observed: malformations of limbs, abnormal fetus movements and cranial nerves (hypomimia, abnormalities in suckling, deglutition, and eye movements).

Animal studies have not demonstrated teratogenicity but have shown fetotoxicity at high doses.

Available data regarding a potential risk of fetal abnormality after an unsuccessful medical abortion are limited and inconclusive; therefore, it is unnecessary to insist on termination of an exposed pregnancy if the woman wishes to continue it. Women should, nevertheless, be informed that due to the unknown risk to the fetus of abortifacient medicines, follow-up is important.

### Breastfeeding

The levels of misoprostol in breast milk are low and decline very rapidly: after 5 hours of a single oral dose of 600 mcg, the levels in breast milk are unmeasurable and the risk to the infant is therefore minimal after a single dose. In practical terms, breast-feeding can be continued.

### Fertility

Adverse effects on male or female fertility or reproduction were observed in rats at doses much higher than the maximum recommended human dose. Adverse effects on fertility or reproduction in humans seem unlikely.

## Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Headache, dizziness, and tiredness have been reported during treatment with misoprostol. Patients should be instructed that, if they experience these symptoms, they should avoid potentially hazardous tasks such as driving and operating machinery.

## Undesirable effects

### Summary of the safety profile

The most commonly reported adverse reactions during treatment are shivering and fever. In general, shivering and fever occur 60–90 minutes after misoprostol administration and are transient and short-lived.

### List of adverse reactions

Safety of a misoprostol formulation has been evaluated in 1,428 women treated for PPH.

The adverse reactions reported in the clinical program are provided below and are classified according to frequency and system organ class. Undesirable effects are ranked under headings of frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency groupings are as follows:

- Very common ( $\geq 1/10$ )
- Common ( $\geq 1/100$  to  $< 1/10$ )
- Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )
- Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )
- Very rare ( $< 1/10,000$ ),
- Frequency not known (cannot be estimated from available data)

Table M-5. Adverse Reactions from Misoprostol

MEDRA SYSTEM ORGAN CLASS	ADVERSE REACTIONS (FREQUENCY)			
	VERY COMMON	COMMON	UNCOMMON	RARE
Nervous System Disorders		Headache Fainting/Dizziness		
Gastrointestinal Disorders	Nausea	Vomiting/Diarrhea		
Skin and subcutaneous tissue disorders				Allergic reaction
General disorders and administration site disorders	Shivering Fever, including temperature $\geq 40^{\circ}\text{C}$ .	Chills	Fatigue	

When used for induction of labor, uterine hyperstimulation and rupture as well as fetal distress may occur.

When used for abortion the following adverse events were reported:



- Uterine cramping, prolonged menstrual-like bleeding, on average for nine days (up to 45 days), incomplete abortion. Rarely, genital tract infection and uterine rupture.

Women should be advised to return for follow-up if they are experiencing prolonged heavy bleeding or fever.

## Overdose

Symptoms linked to overdose of misoprostol are fever, blood pressure disorders, nausea, abdominal cramping and tremors. There is no known antidote for misoprostol overdose. In the event of an overdose, the patient should be closely monitored.

## PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of misoprostol products. When assessing the complete quality/CMC documentation, assessors should consider the following information on misoprostol tablets.

### API

Misoprostol API is viscous oil, which must be stored below -20°C. It is extremely susceptible to degradation. Research established that a dispersion of misoprostol in hydroxypropyl methyl cellulose (HPMC) was considerably more stable than the pure misoprostol oil. Conventional tablets can be prepared from the solid misoprostol dispersion, with a shelf life of several years at room temperature.

As of June 2022, only one manufacturer of misoprostol dispersion (1:100 in HPMC) has been prequalified by the WHO PQP.

Table M-6. Manufacturer of WHO-Prequalified Misoprostol API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RE-TEST PERIOD OR SHELF-LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-226	Piramal Healthcare UK Ltd	Piramal Healthcare UK Ltd Whalton Road Morpeth Northumberland NE61 3YA, UK	Store in a refrigerator (2°C to 8°C), protect from moisture, protect from light	60 months	12/17/2015

Only one manufacturer of misoprostol API has obtained the certificate of suitability to monographs of the European Pharmacopeia (CEP), confirming its suitable quality for use in medicinal product.

Table M-7. Manufacturer of Misoprostol API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Misoprostol (monograph number I731)	Piramal Healthcare UK Ltd GB NE61 3YA Morpeth, UK	RI-CEP 2010-121-Rev 01	1/20/2017	Chemistry

Other manufacturers of misoprostol API should provide evidence for GMP compliance and API quality documentation as per the WHO guidelines.<sup>3</sup>

The specifications of misoprostol API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP). The specifications of misoprostol dispersion should be in line with a pharmacopeial monograph (Ph.Int. or USP).

## Excipients

Excipients must conform to pharmacopeia monographs. The recommendations for the selection of key excipients are listed below.

### Filler: microcrystalline cellulose

Selection of the microcrystalline cellulose is likely to be important for tablet stability over the course of its shelf life. Because almost nine times the amount of microcrystalline cellulose is used compared to misoprostol 1% HPMC dispersion, the water content of this excipient will contribute most to the overall water content of the finished product.

Selected grades of Avicel® microcrystalline cellulose (FMC biopolymer) and their water content are shown below. Other manufacturers of microcrystalline cellulose make products with similar specifications.

Table M-8. Grades of Avicel® Microcrystalline Cellulose and their Water Contents

PRODUCT GRADES	NOMINAL PARTICLE SIZE, µM	MOISTURE %	LOOSE BULK DENSITY G/mL
Avicel PH-102	100	3.0–5.0	0.28–0.33
Avicel PH-103	50	NMT 3.0	0.26–0.31
Avicel PH-113	50	NMT 2.0	0.27–0.34
Avicel PH-112	100	NMT 1.5	0.28–0.34

Two factors determine the selection of the grade of microcrystalline cellulose to use in the production:

- Whether a drying stage is to be incorporated
  - If the microcrystalline cellulose will be dried to a low-moisture specification, then consider a microcrystalline cellulose with particle size that is compatible with dispersion for effective blending, and rheology of bulk and compression results (hardness, friability, low weight variation, etc.). The initial water content of the excipient will influence the drying time, but the rate of moisture absorption after drying should also be taken into account.
  - If no drying stage is incorporated, then a microcrystalline cellulose with the lowest moisture content, such as PH-112 (moisture not more than 1.5%), would seem appropriate to use.
- Grade required for most efficient blending and tablet pressing
  - Selection of a grade that will result in more effective blending with the API may be critical to ensure content uniformity, rheology properties, and tablet pressing

<sup>3</sup> WHO. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in WHO Expert Committee on Specifications for Pharmaceutical Preparations. 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

results. This is especially true for misoprostol 200 mcg tablets because the small amount of misoprostol API relative to the microcrystalline cellulose can make uniform blending challenging.

### Disintegrant: sodium starch glycolate

This material is used to promote disintegration of the tablet and is recommended for use in tablets prepared by a dry compression process. Sodium starch glycolate is hygroscopic in nature. It swells rapidly when it comes in contact with water, resulting in rapid disintegration and dissolution. The European and US Pharmacopeias differentiate the properties of sodium starch glycolate types A, B and C as summarized below.

Table M-9. Properties of Sodium Starch Glycolate

TEST	TYPE A	TYPE B	TYPE C
pH	5.5–7.5	3.0–5.0	5.5–7.5
NaCl	Max 7%	Max 7%	Max 1%
LOD	Max 10%	Max 10%	Max 7%
Assay Na	2.8–4.2%	2.0–3.4%	2.8–5.0%

Sodium starch glycolate type A with low moisture content should be used in the manufacture of misoprostol tablets.

## Manufacturing process

### Environmental conditions and moisture exclusion

Environmental conditions during all stages of production, from weighing, blending, compression, and blistering should be carefully controlled to exclude moisture. Since misoprostol tablets are manufactured as a typical dry blend, much can be prepared in an 8-hour shift, from weighing of starting materials to cold aluminum formed blister packing.

Closed and continuous production systems are preferred to open and discontinuous processes.

The selection of the environmental temperature and relative humidity conditions may depend on the length of each of the stages of production, the time between stages, and how blended materials or bulk tablets are packed and stored.

If specific stages of production such as compression or blistering are expected to take more than several hours, consideration should be given to reducing the relative humidity for the stages to reduce overall exposure to moisture. Alternatively, storage of amounts of material needed for less than one hour of operations in sealed containers containing a desiccant should be considered. The use of desiccant should be studied carefully because in high–relative humidity conditions and/or prolonged storage it might create a microenvironment of high moisture and increase the risk of transfer of moisture to the bulk.

If desiccant is used to protect the bulk product, manufacturers should use airtight containers (aluminum, stainless steel, or other suitable canister) and replace the desiccant bags every time the canister is opened, or with frequency, to prevent moisture transfer. Desiccant bags should be dedicated and regenerated to prevent cross-contamination with other chemicals.

*Good practice:* suggested conditions for production are as follows:

- Temperature: not more than 25°C.
- Relative humidity: 30–50% depending on the length of time bulk blend or tablets are exposed to the atmosphere.
- Manufacturers should validate their production processes at the temperature and humidity levels selected for manufacture.

### In-process controls

In a typical 200-mcg misoprostol tablet, 20 mg of the misoprostol 1% dispersion in HPMC is mixed with 180 mg of excipients. However, the actual content of misoprostol in the final product (200 mcg), is 0.1% the weight of a 200-mg tablet. The very low ratio of pure drug substance to the excipients can present a challenge to uniform blending, which will be critical to ensure good uniformity of content of finished product.

A validated blending process is critical, but sampling of the final blend from multiple locations in the bulk blend should be conducted for every batch to ensure the consistency of the blending process.

*Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D “Guideline for Elemental Impurities”. Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*

### Hold times in production

Short holding times between stages of production reduce potential exposure to moisture. Validation of holding times longer than 8 hours should be studied with caution, because one of the critical factors is the acceptance criteria. The main objective of this manual is to reduce variability within a batch and among batches, and to aim for the most stringent limits to assure not only homogeneity within a batch and among batches but also to improve the shelf life of the finished product.

*Good practice:* All production processes from blending to blistering should be carried out in as short a time as possible to reduce the possibility of exposure to moisture during production.

### Storage conditions during production

The best practice is to blend, tablet-press, and foil-pack misoprostol tablets in a single day’s operation. Where this is not possible, amounts of material required for a one-hour operation should be packed in virgin bags with the best possible barrier to moisture. If thermo-sealing is not possible, plastic ties can be used. Double bagging is better than single bags and a sturdy secondary container (plastic or stainless steel drum) with tight sealing and light protection is preferred.

The inclusion of a desiccant for storage is recommended, but the use of desiccants between bags or inside the drums should be studied with care to avoid possible release of moisture from desiccant to bulk or tablets.

## Packaging

Misoprostol tablets in certain low- and middle-income countries are likely to be subjected to conditions of high humidity and temperature. Packaging that reduces water vapor transmission should ensure stability of the medicine during its shelf life. At 38°C and 90% relative humidity, cold-form aluminum completely prevents water vapor transmission. PVC, by contrast, has much higher water vapor transmission rate (2.4–4 g/m<sup>2</sup>/day) under these conditions, which may occasionally be

experienced during storage in hot and humid countries. Different grades of PVC/PVDC are also more protective than PVC, but not as protective as aluminum. The table below shows water vapor transmission rates (WVTR) for selected packaging.

Table M-10. Comparative Moisture Barrier Properties of Blister Packaging Materials

TYPICAL WVTR G/M <sup>2</sup> /DAY 38°C/90%RH	
Cold-form aluminum	0.00
PVC/80g PVDC	0.31
PVG/60g PVDC	0.47–0.6
PVC/40g PVDC	0.7–0.75
PVC	2.4 –4.0

*Good practice: Misoprostol tablets should be packed in an aluminum-aluminum blister pack to reduce the risk of exposure to moisture in humid environments.*

Suitability of the aluminum foil should be demonstrated, including:

- Safety: declarations as to compliance with appropriate food additive regulations (e.g., USFDA or EU regulations)
- Protection: WVTR and light transmission (LT) rate as per USP<671>
- Compatibility: accelerated and long-term stability data for the packaged finished products

## Bioequivalence requirements

A randomized, single-blind, single-dose, two-treatment, two-period, crossover bioequivalence study in healthy adult female subjects under fasting conditions is required. An appropriate comparator product is Cytotec® (misoprostol 200 mcg tablet, Searle/Pfizer), purchased from an SRA market.

Misoprostol has a range of therapeutic indications, employing a variety of routes of administration. However, it should be noted that the bioequivalence between the proposed and comparator products demonstrated following oral administration cannot be extrapolated to the other routes of administration. To obtain the full range of indications and routes of administration for a misoprostol product, in addition to the bioequivalence study employing oral administration as described above, the following data are required:

- Data from a single-dose, crossover bioequivalence study employing sublingual administration. Proof of bioequivalence in this study would be considered sufficient information to grant indications employing sublingual and buccal routes of administration.
- Pharmacokinetic data (not necessarily a bioequivalence study) showing that, following vaginal administration, the proposed product produces in vivo misoprostol concentrations with a mean maximal concentration (C<sub>max</sub>) of at least 200 pg/mL (normalized for an 800-mcg dose) and an extent of absorption (area under the curve [AUC]) that exceeds that observed following oral administration of the product (on a dose-normalized basis).
- Further, additional dissolution data will be needed to accept the product for the indication of “induction of labor” due to the required administration of fractional doses.

# MAGNESIUM SULFATE

INJECTION, 500 MG/ML IN 2-ML  
AND 10-ML AMPOULE

## GENERAL PRODUCT INFORMATION

Pre-eclampsia and eclampsia is the second-leading cause of maternal death in low- and middle-income countries. It is most often detected through the elevation of blood pressure during pregnancy, which can be followed by seizures, kidney and liver damage, and maternal and fetal death, if untreated.

Magnesium sulfate is recognized by WHO as the safest, most effective, and lowest-cost medicine for treating severe pre-eclampsia and eclampsia. It is also considered an essential medicine by the UN Commission on Life-Saving Commodities for Women and Children. Other anticonvulsant medicines, such as diazepam and phenytoin, are less effective and riskier. Magnesium sulfate should be the only treatment of severe pre-eclampsia and eclampsia and should be procured over other anticonvulsants and made available in all health facilities to help lower maternal death rates and improve overall maternal health.

Additionally, WHO recommends the use of magnesium sulfate for women at risk of imminent preterm birth before 32 weeks of gestation for prevention of neurological complications (neuroprotection). Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours. Magnesium sulfate should be administered regardless of the cause for preterm birth and the number of babies in utero.<sup>1</sup>

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<sup>1</sup> WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization; 2015. Available from: [http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988\\_eng.pdf?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1)

## KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO or approved by a SRA for magnesium sulfate injection and those with a proven record of quality products.
2. Procurers need to focus on product quality to ensure that it is sterile and safe for patient use as magnesium sulfate is an injectable medicine.

## KEY QUALITY CONSIDERATIONS

### **Product specification**

Products that are procured must comply with pharmacopeial specifications, such as those of the International Pharmacopoeia, US Pharmacopeia, and British Pharmacopoeia, as detailed in the “Supply” section 4 below.

### **Packaging and labeling**

The container-closure system (ampoule) must be sufficient to preserve sterility during the shelf life of the product.

Procurement of 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations as per the WHO EML is recommended. The WHO EML recommends magnesium sulfate 500 mg/mL (50% w/v) in 2-mL and 10-mL ampoule presentations, for convenient use in both Pritchard (IV/IM) and Zuspan (IV/IV) dosing regimens for the treatment of eclampsia and severe pre-eclampsia. Some SRA-approved products are presented in different packaging and/or concentrations, which require an adaptation of the dilution process during dosage preparation. The additional burden of recalculation is time-consuming and can introduce potential errors.

Additional information about the packaging and labeling can be found in the Annex.

### **Storage, transportation, and distribution**

Magnesium sulfate must be stored safely to ensure that ampoules do not break or leak, which would compromise their sterility. Products do not need to be maintained in the cold chain.



<b>Name of the Medicinal Product</b>	Magnesium sulfate injection
<b>Chemical Name</b>	Magnesium sulfate (1:1) heptahydrate
<b>Chemical Structure</b>	MgSO <sub>4</sub> , 7H <sub>2</sub> O
<b>Pharmaceutical Form</b>	Sterile solution for injection A clear, colorless solution
<b>Qualitative and Quantitative Composition</b>	Magnesium sulfate injection is a sterile solution of magnesium sulfate heptahydrate in water for injection. It contains 500 mg of magnesium sulfate heptahydrate per mL (50% w/v), approximately 2 millimoles magnesium ions (Mg <sup>2+</sup> ) per mL 1 ampoule (2 mL) contains 1,000 mg of magnesium sulfate heptahydrate. 1 ampoule (10 mL) contains 5,000 mg of magnesium sulfate heptahydrate.  List of typical excipients: – Water for injections – Sulfuric acid/Hydrochloric acid and/or sodium hydroxide, for pH adjustment
<b>Packaging and Presentation</b>	The WHO Essential Medicines List includes two presentations: 500 mg/mL in 2-mL ampoule (equivalent to 1 g in 2 mL; 50% w/v) and 500 mg/mL in 10-mL ampoule (equivalent to 5 g in 10 mL; 50% w/v). These ampoules would need to be mixed with IV solution to dilute to 20 percent solution for an IV loading dose.

## SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved or ERP-recommended products, medicines from the trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in [Module II](#).

### WHO-prequalified products

As of June 2022, there are seven magnesium sulfate injections prequalified by the WHO PQP, as shown in the table below. It is recommended to check the updated information at the time of procurement, which can be found at <https://extranet.who.int/pqweb/medicines/prequalified-lists/finished-pharmaceutical-products>.

## Magnesium Sulfate

Table MS-11. List of WHO-Prequalified Magnesium Sulfate Injection

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
RH062(a)	Inresa Arzneimittel GmbH, Obere Hardtstraße 18, 79114, Freiburg, Germany	FPP manufacturing site: Laboratoire Renaudin, ZA Errobi, 64250, Itxassou, France  API manufacturing site: – K+S KALI GmbH, Bertha-von-Suttner-Strasse 7, Kassel, Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 50%	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 50's 10 mL x 100's	15-Aug-16	3 years	Do not store above 25°C.
RH063	AS Kalceks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma SRO, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey  API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (2 mL)	Ampoule: type I glass 2 mL x 10's 2 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.
RH064	AS Kalceks, Krustpils iela 71E, Rīga, LV-1057, Latvia	FPP manufacturing site: – HBM Pharma sro, Sklabinska 30, Martin, 036 80, Slovakia – Mefar Ilac Sanayii A.S., Ramazanoglu Mah. Ensar Cad. No: 20, Kurtkoy-Pendik, Istanbul, TR-34906, Turkey	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's 10 mL x 10's 10 mL x 100's	4-Jul-17	5 years	Do not store above 30°C.

## Magnesium Sulfate

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
		API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic					
RH072(a)	Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal	FPP manufacturing site: Labesfal, Laboratorios Almiro SA, Unit 2, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal  API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass, colorless 10 mL x 50's	19-Jun-18	5 years	Do not store above 30°C.
RH073(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom  API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 50% w/v, 2 mL	Ampoule; neutral type I glass 2 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.
RH077(a)	Aurum Pharmaceuticals Ltd, Bampton Road, Harold Hill,	FPP manufacturing site: Macarthys Laboratories Limited, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, United Kingdom	Solution for injection 50% w/v, 10 mL	Ampoule; neutral type I glass 10 mL x 10's	12-Dec-17	3 years	Do not store above 30°C.

Magnesium Sulfate

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
	Romford, Essex, RM3 8UG, United Kingdom	API manufacturing site: – K+S KALI GmbH, Werk Werra, Hattorfer Strasse, 36269, Philippsthal (Werra), Germany – Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic					
RH086	Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine	FPP manufacturing site: Joint-Stock Company Halychpharm, 6/8, Opryshkivska Str., Lviv, 79024, Ukraine  API manufacturing site: Macco Organiques, S.R.O, Zahradni 1938/46c, Bruntál, 792 01, Czech Republic	Solution for injection 500 mg/mL (10 mL)	Ampoule: type I glass 10 mL x 5's x 2	16-Mar-20	4 years	Do not store above 30°C. Do not freeze.

(a) Indicates SRA-approved product that has been prequalified based on abbreviated assessment.

## SRA-approved products

Table MS-12. Examples of SRA-Approved Magnesium Sulfate 500 mg/mL in 2-mL and 10-mL Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Magnesium sulfate 50% w/v solution for injection or infusion	UK MHRA	Torbay and South Devon NHS Foundation Trust, UK	PL 13079/0004	Glass ampoule: 2 mL, 10 mL	3 years	This medicinal product does not require any special storage conditions.
Magnesium Sulfate 50%w/v Solution for Injection	UK MHRA	Aurum Pharmaceuticals Ltd, UK	PL 12064/0013	Glass ampoule: 2 mL, 10 mL	3 years	Do not store above 25°C.
Magnesium Sulfate 50% w/v Solution for Injection/ Infusion	UK MHRA	AS KALCEKS, Latvia	PL 47015/0010	Glass ampoule: 2 mL, 10 mL	30 months	Do not freeze.
Magnesium sulfate 50% w/v solution for injection	Swissmedic	Grosse Apotheke Dr. G. Bichsel AG, Switzerland	56394	Glass ampoule: 2 mL, 10 mL	Not specified	Store at room temperature (15–25°C).

Note: Magnesium sulfate injection 50% products that are approved by the US FDA (e.g. those supplied by Fresenius Kabi, Hospira Inc, Exela Pharma) are not included in the list above, as they are available in glass vials of 10 mL, 20 mL, and 50 mL different from the presentations as per the WHO recommendation.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, it should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- UK MHRA: <https://products.mhra.gov.uk/>
- EU regulatory authorities: [https://ec.europa.eu/health/documents/community-register/regca\\_en](https://ec.europa.eu/health/documents/community-register/regca_en)
- Swissmedic: <https://www.swissmedicinfo.ch/>
- Health Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>.

## Related products

Other formulations of magnesium sulfate injection on the market include the following products:

### **Magnesium sulfate 10% w/v**

Indicated in adults, adolescents, and children for: i) treatment of magnesium deficiency in proven hypomagnesemia; and ii) prevention and treatment of hypomagnesemia in patients receiving total parenteral nutrition

Indicated in parturients for: i) control and prevention of seizures in severe pre-eclampsia; and ii) control and prevention of recurrent seizures in eclampsia.

### **Magnesium sulfate 20% w/v**

Indicated for prevention of further seizures associated with eclampsia, and for treatment of magnesium deficiency in hypomagnesemia where the oral route of administration may be inappropriate.

## STORAGE, STABILITY, AND DEGRADATION



Magnesium sulfate is very stable at ambient temperatures and is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Shelf life: 3–5 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage condition: Do not store above 30°C. Do not freeze.

The shelf life and storage condition of each WHO-prequalified and SRA-approved product can be found in Table MS-1 and Table MS-2 above respectively.

## PRODUCT SPECIFICATIONS



The product must meet pharmacopeial specifications, such as those of the International Pharmacopeia, US Pharmacopeia, and British Pharmacopeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the three pharmacopeias are the same, except for the assay and bacterial endotoxin limits.

Table MS-13. International Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	As per IP monograph of magnesium sulfate injection
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	2.1 General identification tests
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	1.13 pH value
Assay	90.0–110.0%	2.5 Complexometric titrations
Bacterial endotoxins	Less than 0.18 IU of endotoxin per mg magnesium sulfate heptahydrate	3.4 Test for bacterial endotoxins
Sterility	Sterile	3.2 Test for sterility
Extractable volume	Comply	5.6 Extractable volume for parenteral preparations
Particulate matter	Comply	5.7 Tests for particulate contamination: subvisible particles

Table MS-14. US Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	USP<191>
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	USP<191>
pH	pH of the injection, diluted to contain 50 mg of magnesium sulfate heptahydrate per mL: 5.5–7.0	USP<791>
Assay	93.0–107.0%	Titration, USP monograph
Bacterial endotoxins	Not more than 0.09 USP endotoxin unit/mg of magnesium sulfate	USP<85>
Sterility	Sterile	USP<71>
Extractable volume	Comply	USP<1>

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Particulate matter	Meet the requirements for small-volume injections	USP<788>

Table MS-15. British Pharmacopeia Specifications for Magnesium Sulfate Injection

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification	Yield the reactions characteristic of magnesium salts	Appendix VI
a) Magnesium		
b) Sulfate	Yields the reactions characteristic of sulfates	Appendix VI
pH	pH of the injection, diluted to contain 5% w/v of magnesium sulfate heptahydrate per mL: 5.5–7.0	Appendix V L
Assay	95.0–105.0%	Titration, BP monograph
Bacterial endotoxins	Comply	Appendix XIV C
Sterility	Sterile	Appendix XVI A
Extractable volume	Comply	Appendix XII C5
Particulate matter	Comply	Appendix XIII A





# PART I: CLINICAL PARTICULARS

## Therapeutic indications

- Prevention of eclampsia in women with severe pre-eclampsia
- Treatment of women with eclampsia
- Prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation)

## Posology, method, and duration of administration

### Severe pre-eclampsia and eclampsia

The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia. For settings where it is not possible to administer the full magnesium sulfate regimen, the use of a magnesium sulfate loading dose followed by immediate transfer to a higher-level health care facility is recommended.

*Note regarding dilution for IV use*

*Magnesium sulfate injection **must** be diluted to a  $\leq 20\%$  solution for intravenous use. Diluents commonly used are 5% glucose solution and 0.9% sodium chloride solution. For a 20% solution, dilute 10 mL of magnesium sulfate injection with 15 mL of diluent.*

*Intravenous dosing should be done using an infusion pump if available.*

*From a microbiological point of view, the reconstituted/diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C, unless reconstitution/dilution (etc.) has taken place in controlled and validated aseptic conditions.*

### Pritchard regimen (IV/IM)

Loading dose (IV and IM):

- Give 4 g IV over five minutes (20 mL of the diluted 20% magnesium sulfate solution).
- Follow promptly with 10 g of 50% magnesium sulfate solution: give 5 g (10 mL of the undiluted 50% solution) in each buttock as a deep IM injection with 1 mL of 2% lidocaine in the same syringe.

Ensure aseptic technique when giving magnesium sulfate deep IM injection. Warn the woman that she will have a feeling of warmth when the magnesium sulfate is given.

If convulsions recur after 15 minutes, give 2 g (10 mL of the diluted 20% magnesium sulfate solution intravenously over 5 minutes.

*Maintenance dose (intramuscular):*

- Give 5 g (10 mL of the undiluted 50% magnesium sulfate solution) with 1 mL of 2% lidocaine in the same syringe by deep IM injection into alternate buttocks every four hours. Continue treatment for 24 hours after birth or the last convulsion, whichever occurs last.

**Zuspan regimen (IV/IV)**

See note above on how to dilute the product to a 20% solution.

*Intravenous administration, using an infusion pump if available:*

Loading dose:

- Give 4 g IV over five minutes (20 mL of the diluted 20% magnesium sulfate solution).
- If convulsions recur after 15 minutes, give 2 g (10 mL of the diluted 20% magnesium sulfate solution) IV over 5 minutes.

Maintenance dose (intravenous):

- Give intravenous infusion 1 g (5 mL of the diluted 20% magnesium sulfate solution) per hour. Continue treatment for 24 hours after childbirth or the last convulsion, whichever occurs last.

Although magnesium toxicity is rare, a key component of monitoring women with severe pre-eclampsia and eclampsia is assessing for signs of magnesium toxicity.

Before administration, it is important to ensure that:

- respiratory rate is at least 16 per minute;
- patellar reflexes are present;
- urinary output is at least 30 ml per hour over 4 hours.

If there are signs of toxicity, the next intramuscular dose should be delayed or the intravenous infusion of magnesium sulfate withheld. Signs indicating the need to withhold or delay maintenance dose of magnesium sulfate are:

- respiratory rate below 16 breaths per minute;
- patellar reflexes are absent;
- urinary output falls below 30 ml per hour over preceding 4 hours.

The antidote (calcium gluconate) should be kept ready. In case of respiratory arrest:

- assist ventilation (mask and bag, anaesthesia apparatus, intubation);
- give calcium gluconate 1 g (10 ml of 10% solution) intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

**Prevention of cerebral palsy in the infant of women at risk of imminent preterm birth before 32 weeks of gestation**

Magnesium sulfate for neuroprotection should only be given if preterm birth is likely within the next 24 hours.

Three intravenous dosing regimens have been used for prevention of cerebral palsy. There is insufficient evidence at present to recommend one over the others:

- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20 minutes, then 1 g (5 mL of the diluted 20% magnesium sulfate solution) per hour until delivery or for 24 hours, whichever comes first.
- 4 g (20 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 30 minutes, or as a single intravenous bolus.
- 6 g (30 mL of the diluted 20% magnesium sulfate solution) infused intravenously over 20–30 minutes, followed by maintenance infusion of 2 g (10 mL of the diluted 20% magnesium sulfate solution) per hour.

When Magnesium sulfate is administered, women should be monitored for clinical signs of magnesium toxicity at least every 4 hours by recording pulse, blood pressure, respiratory rate, and deep tendon (for example, patellar) reflexes.

### **Use in patients with renal impairment**

In patients with mild to moderate renal impairment, dosage should be reduced. For safe use, vigilance is advised for clinical signs of magnesium toxicity (i.e. respiratory rate falling below 16 /min, absent patellar reflexes, urine output below 30 ml per hour in preceding 4 hours). Monitoring of blood magnesium levels may also be helpful.

In patients with severe renal impairment, magnesium sulfate is contraindicated.

### **Contraindications**

- Hypersensitivity to the active substance, its salts or to any of the excipients
- Heart block
- Severe renal impairment

### **Special warnings and precautions for use**

Clinical indicators of a safe regimen include:

- respiratory rate is above 16 breaths per minute;
- patellar reflexes are present;
- urinary output is above 30 ml per hour over preceding four hours.

When magnesium sulfate is used in pregnant women, fetal heart rate should be monitored (see also “Fertility, pregnancy and lactation” section below).

Parenteral magnesium sulfate should be used with caution in patients with myasthenia gravis.

Magnesium sulfate should be administered with extreme caution in patients receiving  $\beta$ -adrenergic agonists, calcium antagonists, CNS depressants, cardiac glycosides and neuromuscular blocking agents (see also “Interaction with other medicinal products and other forms of interaction” section below).

Alcohol abuse increases the excretion of magnesium resulting in decreased magnesium levels.

Parenteral magnesium sulfate administration is contraindicated in patients with severe renal impairment (see also “[Contraindications](#)” section above). It should be used with caution in less severe degrees of renal impairment.

## Interaction with other medicinal products and other forms of interaction

Extreme caution must be used when  $\beta$ -adrenergic agonists and calcium-channel blocking agents (e.g. nifedipine) are administered concomitantly with magnesium sulfate due to a risk of serious adverse maternal effects (reduced heart rate, contractility, left ventricular systolic pressure and neuromuscular blockade).

When CNS depressants (e.g. barbiturates, opiates, general anaesthetics) are administered concomitantly with magnesium sulfate, dosage of these medicines must be carefully adjusted because of the additive central depressant effect.

Magnesium sulfate should be used with extreme caution in patients taking digoxin, as it may cause serious changes in cardiac conduction, including heart block.

Concomitant use of neuromuscular blocking agents with magnesium sulfate leads to excessive neuromuscular blockade; these medicines should be administered concomitantly only with caution. Patients should be monitored for respiratory depression.

Magnesium sulfate is incompatible with alkali hydroxides (forming insoluble magnesium hydroxide), alkali carbonates (forming insoluble magnesium carbonate) and salicylates. The activities of antibiotics such as streptomycin and tetracycline are inhibited by magnesium ions. Use with diuretics, aminoglycosides (such as gentamycin, tobramycin amphotericin B), and nephrotoxic immunosuppressants (such as ciclosporin) or cytotoxics (such as cisplatin) may increase the risk of adverse effects. It is also advised that magnesium sulfate not be used in conjunction with benzylpenicillin, nafcillin, polymyxin, dobutamine, or procaine (novocaine).

## Fertility, pregnancy and lactation

### Pregnancy

Safety in human pregnancy has not been established, however, in the medical emergency of a patient having eclampsia, magnesium sulfate can be administered to relieve this condition, which may be life threatening to both mother and baby.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided.

Magnesium sulfate can cause skeletal adverse effects in the child when administered continuously for more than 5 to 7 days to pregnant women. There are retrospective epidemiological studies and case reports documenting fetal adverse effects including hypocalcaemia, skeletal demineralization, osteopenia and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5 to 7 days. The clinical significance of the observed effects is unknown.

If prolonged or repeated exposure to magnesium sulfate occurs during pregnancy, monitoring of neonates for abnormal calcium or magnesium levels and skeletal adverse effects should be considered.

## Breastfeeding

Magnesium sulfate is excreted in negligible amounts into breast milk, therefore the use of magnesium sulfate is compatible with breast-feeding.

Postpartum use of intravenous magnesium sulfate for longer than 6 hours appears to delay the onset of lactation.

## Fertility

No studies and/or data are available on the effects on fertility.

## Effects on ability to drive and use machines

No studies have been carried out on the ability to drive and use machines.

## Undesirable effects

Adverse events related to treatment are listed below. They reflect published literature data, but reliable information on frequency is not available.

Table MS-16. Adverse Events Related to Treatment with Magnesium Sulfate Injection

SYSTEM ORGAN CLASS	ADVERSE DRUG REACTION
Immune system disorders	Hypersensitivity reactions, flushing
Metabolism and nutrition disorders	Thirst
Nervous system disorders	Double vision
Psychiatric disorders	Drowsiness, confusion, slurred speech
Cardiac disorders	ECG changes (prolonged PR, QRS and QT intervals), bradycardia, cardiac arrhythmias, cardiac arrest and coma
Vascular disorders	Hypotension
Gastrointestinal disorders	Nausea, vomiting
Respiratory, thoracic, and mediastinal disorders	Respiratory depression*
Musculoskeletal and connective tissue disorders	Loss of tendon reflexes due to neuromuscular blockade, muscle weakness
General disorders and administration site conditions	Pain with intramuscular injection
Investigations	Electrolyte/fluid abnormalities (hypophosphatemia, hyperosmolar dehydration), hypocalcaemia

\* There is a risk of respiratory depression when magnesium sulfate is administered concomitantly with high doses of barbiturates, opioids or hypnotics (see also "Interaction with other medicinal products and other forms of interaction" section above).

## Overdose

### Symptoms of intoxication

Magnesium intoxication is manifested by a sharp drop in blood pressure and respiratory paralysis. Excessive parenteral doses of magnesium salts lead to the development of hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade.

Other symptoms and signs of hypermagnesaemia may include nausea, vomiting, flushing, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, low heart rate, cardiac arrhythmias, electrolyte/fluid abnormalities. In severe cases coma and cardiac arrest may occur.

Patients with renal failure and metabolic derangements develop toxicity at lower doses.

### **Treatment of intoxication**

Assisted ventilation.

Calcium gluconate 1 g (10 mL of 10% solution) given intravenously slowly over 3 minutes, until respiration begins to counteract the effect of magnesium sulfate.

Dialysis may be necessary in patients with renal impairment or severe hypermagnesemia.

## PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of magnesium sulfate injection products. When assessing the complete quality/CMC documentation, assessors should consider the following information on magnesium sulfate injection.

### API

As of June 2022, no magnesium sulfate API is prequalified by the WHO PQP.

There are two manufacturers of magnesium sulfate API that have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal products.

Table MS-17. Manufacturers of Magnesium Sulfate API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Magnesium sulfate heptahydrate (monograph number 44)	Macco Organiques, SRO CZ 792 01 Bruntál, Czech Republic	R0-CEP 2016-148-Rev 00	10/20/2017	Chemistry
Magnesium sulfate heptahydrate (monograph number 44)	PQ CORPORATION, Malvern, USA	R0-CEP 2018-109-Rev 00	6/17/2020	Chemistry

Other manufacturers of magnesium sulfate API should provide evidence for GMP compliance. However, magnesium sulfate is an atypical API; the manufacturing process and controls are not typically designed to meet API GMP. As an alternative, there should be a clear specification, the site should have been audited, changes should be controlled, and appropriate checks should be made on incoming goods.

The specifications of magnesium sulfate API should be in line with a pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic if not included in that monograph, as well as tests/limits for bacterial endotoxins. Such additional tests may be based on another pharmacopeial monograph (Ph.Int., Ph.Eur./BP, or USP).

### Excipients

The excipients of magnesium sulfate injection include water for injection and sulfuric acid/hydrochloric acid and/or sodium hydroxide for pH adjustment. There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.



## Manufacturing process

Magnesium sulfate injection is a straightforward product to manufacture, but the main quality concern is the sterilization process and sterility of the facility where it is made.

The manufacturing process of magnesium sulfate injection is a standard process—conducted under appropriate aseptic conditions, including the steps of preparation of the solution with adjustment of pH, pre- and sterile filtration, and filling and sealing of the ampoules. Finally, steam sterilization by autoclaving of the filled ampoules is performed. The headspace of the ampoules should be replaced with nitrogen during the filling process to prevent oxidation of the API. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacture.

For the sterilization process using an autoclave, details such as F0 range, temperature range and peak dwell time for the FPP and the container-closure system should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

*Note: The risk for potential presence of elemental impurities in the finished drug product needs to be assessed according to the ICH Q3D “Guideline for Elemental Impurities”. Elemental impurity sources include the API, excipients, utilities in direct contact with the product or manufacturing equipment (compressed air, water, etc.), the manufacturing equipment and the container closure system. Depending on the risk assessment and results from batches tested for the relevant elemental impurities, routine testing of the final product may not be necessary.*

## Packaging

Neutral type I glass ampoule should be used.

Suitability of the container should be demonstrated, including the following properties.

### Safety

- The material must meet compendial requirements such as USP<660> and USP<I660>. Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

### Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of the product manufacture

### Compatibility

- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers such as PVC may also need to be demonstrated.

## Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and the same or similar excipients in comparable concentrations as in the comparator product.

The appropriate comparator product is magnesium sulfate 500 mg/mL (solution for injection, Fresenius Kabi, USA). The composition of the proposed product should be the same as the comparator product.