ANNEX I

LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Belgium	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Denmark	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Estonia	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Finland	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
France	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Germany	Contragest GmbH Pharmavertrieb Kelsterbacher Str. 28 D-64546 Walldorf-Moerfelden Germany	Mifegyne	200 mg	Tablet	Oral use

Greece	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Latvia	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Luxembourg	Exelgyn S.A. 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Norway	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Spain	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
Sweden	Exelgyne 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use
The Netherlands	Bipharma B.V. Postbus 151 1380 AD Weesp The Netherlands	Mifegyne	200 mg	Tablet	Oral use
UK	Exelgyn 216 Boulevard St Germain, 75 007 Paris France	Mifegyne	200 mg	Tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARYIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING MIFEPRISTONE (see Annex I)

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors. In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction inducing action of prostaglandin. In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

France requested the CHMP to give its opinion on the benefit/risk profile of mifepristone considering the efficacy and safety concerns with regards to the use of the approved dose of 600 mg mifepristone in the indication of "medical termination of developing intra-uterine pregnancy in sequential use with prostaglandin analogue" as compared to the use of a 200 mg mifepristone dose. In addition, France had some concerns in relation to the safe use of mifepristone.

In view of the available clinical data including literature and international clinical guidelines, the CHMP concluded on the posology of mifepristone to be used in combination with a prostaglandin analogue (gemeprost or misoprostol) in the indication of "*medical termination developing intra-uterine pregnancy in sequential use with prostaglandin analogue (gemeprost or misoprostol) up to 63 days of amenorrhea*".

The CHMP confirmed the use of a 600 mg dose of mifepristone with 400 µg of oral misoprostol or 1 mg gemeprost per vaginam for termination of pregnancies up to 49 days, and extend the use of the 600 mg dose in combination with 1 mg gemeprost per vaginam for termination of pregnancies up to 63 days of amenorrhea.
Additionally the CHMP recommended an alternative dose of mifepristone, a 200 mg dose, in combination with 1 mg gemeprost per vaginam for termination of pregnancies up to 63 days of amenorrhea. Based on the available published data the CHMP is of the opinion that, in combination with mifepristone, gemeprost per vaginam is a more potent prostaglandin than oral misoprostol. Furthermore although data available on the combination of mifepristone 200 mg + gemeprost 1 mg are limited, the CHMP considers that similar high efficacy rates in terms of complete abortion and on-going pregnancies were obtained as noted for the combination of mifepristone 600 mg + gemeprost 1 mg.

Based on non-comparative studies the CHMP is of the opinion that the efficacy in terms of success rate is comparable between the doses of 200 mg and 600 mg of mifepristone when used with 1 mg gemeprost per vaginam for medical abortion up to 49 days of amenorrhea and between 50 and 63 days of menorrhea. However in terms of ongoing pregnancy, the CHMP considers that it is acceptable to retain the 600 mg mifepristone dose for termination of pregnancy up to 49 days of gestation when combined with 400 µg misoprostol oral tablets; based on 3 non comparative studies, the CHMP does not support consistent efficacy of mifepristone 200 mg in combination with misoprostol 400 µg orally.

With regards to the safe use of the procedures for termination of pregnancies and related use of prostaglandin analogue such as misoprostol tablets, the CHMP confirms that oral misoprostol can only be used with a 600 mg dose of mifepristone for medical abortion up to 49 days of amenorrhea. Some very rare cases of fatal toxic shocks have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. The CHMP therefore recommends that clinicians respect the approved regimen of 600 mg mifepristone and 400 µg of oral misoprostol, and reiterates the risks related to this non-approved practice.

Subsequently, the CHMP harmonised the indications of mifepristone in the EU.

The CHMP concluded on these observations that the efficacy outcomes of mifepristone depend on the duration of amenorrhea, the type of prostaglandin and the related route of administration.

With regards to the safety, the CHMP agreed on some additional warnings and precautions for use in the SPC such as the risk of heavy bleeding, concomitant medications, interactions, risks related to certain populations, infections, and the follow-up of patients going through termination of pregnancies. The SPC has been thoroughly revised and changes in the package leaflet are reflected accordingly.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing mifepristone.

- The Committee considered that mifepristone is effective in the indication of *"medical termination developing intra-uterine pregnancy in sequential use with prostaglandin analogue (gemeprost or misoprostol) up to 49 days of amenorrhea"* when given 200 mg or 600 mg mifepristone + 1 mg gemeprost or 600 mg mifepristone + 400 µg misoprostol. The Committee also considered that mifepristone is effective in the indication of *"medical termination developing intra-uterine pregnancy in sequential use with prostaglandin analogue (gemeprost or misoprostol) between 50 and 63 days of amenorrhea"* when given 200mg or 600 mg mifepristone + 1 mg gemeprost.

- The Committee acknowledged that very rare cases of fatal toxic shock caused by Clostridium sordellii endometritis, presenting without fever or other obvious symptoms of infection have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. In view of the available data the CHMP concluded that a potential association with the use of mifepristone can be ruled out but information in this regard was included in the sections 4.4 and 4.8 of the SPC.
  In addition, some information with regards to the safety of the product was added to the SPC such as the risk of heavy bleeding, concomitant medications, interactions, risks related to certain populations, infections, and the follow-up of patients going through termination of pregnancies.

- The Committee, as a consequence, considered the benefit/risk balance of medicinal products containing mifepristone to be favourable in the indication of *"medical termination developing intra-uterine pregnancy in sequential use with prostaglandin analogue (gemeprost or misoprostol) up to 63 days of amenorrhea"*.

The CHMP concluded that the benefit/risk balance of mifepristone containing medicinal products in the agreed indications is favourable.

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summaries of Product Characteristics and Package leaflets are set out in Annex III.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mifegyne 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.
For a full list of excipients, see section 6.1
[to be completed nationally]

3. PHARMACEUTICAL FORM

Tablet.
[To be completed nationally]

4. CLINICAL PARTICULARS

For termination of pregnancy, Mifegyne and the prostaglandin can only be prescribed and administered in accordance with the countries national laws and regulations.

4.1 Therapeutic indications

1- Medical termination of developing intra-uterine pregnancy.

In sequential use with a prostaglandin analogue, up to 63 days of amenorrhea**.**

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

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

4- Labour induction in foetal death in utero.
In patients where prostaglandin or oxytocin cannot be used.

4.2 Posology and Method of Administration

1- Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

- Up to 49 days of anenorrhea:

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) is taken in a single oral dose,
followed 36 to 48 hours later, by the administration of a prostaglandin analogue; misoprostol 400 µg orally, or gemeprost 1 mg per vaginam.

Alternatively, 200 mg of mifepristone can also be used in a single oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam (see section 5.1. pharmacodynamic properties)

- Between 50-63 days of amenorrhea

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) is taken in a single oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam.
Alternatively, 200 mg of mifepristone can also be used in a single oral dose, followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg per vaginam (see section 5.1. pharmacodynamic properties)

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

200 mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single oral dose,
36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4- Labour induction in foetal death in utero

600 mg of mifepristone (e.g. 3 tablets of 200 mg each) in a single oral daily dose, for two consecutive days.

Labour should be induced by the usual methods if it has not started within
72 hours following the first administration of mifepristone.

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

IN ALL INDICATIONS

- chronic adrenal failure,
- hypersensitivity to the active substance or to any of the excipients,
- severe asthma uncontrolled by therapy,
- inherited porphyria.

In the indication: medical termination of developing pregnancy

- pregnancy not confirmed by ultrasound scan or biological tests,
- pregnancy beyond 63 days of amenorrhea,
- suspected extra-uterine pregnancy,
- contra-indication to the prostaglandin analogue selected.

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test,
- pregnancy of 84 days of amenorrhea and beyond

- suspected extra-uterine pregnancy.

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

- contra-indications to the prostaglandin analogue selected

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

4.4 Special warnings and special precautions for use

Warnings

In the absence of specific studies, Mifegyne is not recommended in patients with:
- ***Renal failure***
- ***Hepatic failure***
- ***Malnutrition***

1- Medical termination of developing intra-uterine pregnancy

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with prostaglandin to be administered at a second visit,
- the need for a follow-up visit (3^{rd} visit) within 14 to 21 days after intake of Mifegyne in order to check for complete expulsion,
- the possible failure of the method, leading to a pregnancy termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of Mifegyne.

The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

- Risks related to the method

- Failures

  The non-negligible risk of failure, which occurs in 1.3 to 7.5 % of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

- Bleeding

The patient must be informed of the occurrence of prolonged vaginal bleeding (an average of about 12 days or more after Mifegyne intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact

and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

A follow-up visit must take place within a period of 14 to 21 days after administration of Mifegyne to verify by the appropriate means (clinical examination, ultrasound scan, and beta-hCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days. If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

Since heavy bleeding requiring hemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

- Infection

Very rare cases of fatal toxic shock caused by Clostridium sordellii endometritis presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication.

2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of Mifegyne must be followed, 36 to 48 hours later and not beyond, by surgical termination.

- Risks related to the method

- Bleeding

The woman will be informed of the risk of vaginal bleeding which may be heavy, following intake of Mifegyne. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.
Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

- Other risks

They are those of the surgical procedure.

3- In all instances

The use of Mifegyne requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy. During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses. To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

Precautions for use

1- In all instances

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.
Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following intake of Mifegyne. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Limited evidence suggests that co-administration of NSAIDs on the day of prostaglandin administration does not adversely influence the effects of mifepristone or the prostaglandin on cervical ripening or uterine contractility and does not reduce the clinical efficacy of medical termination of pregnancy.

2- Medical termination of developing intra-uterine pregnancy

Rare but serious cardiovascular accidents have been reported following the intra muscular administration of prostaglandin analogue. For this reason, women with risk factors for cardiovascular disease or established cardiovascular disease should be treated with caution.

Method of prostaglandin administration

During intake and for three hours following the intake, the patient should be monitored in the treatment centre, in order not to miss possible acute effects of prostaglandin administration. The treatment centre must be equipped with adequate medical facilities.

On discharge from the treatment centre all women should be provided with appropriate medications as necessary and be fully counselled regarding the likely signs and symptoms she may experience and have direct access to the treatment centre by telephone or local access.

3- For the sequential use of Mifegyne - Prostaglandin, whatever the indication

The precautions related to the prostaglandin used should be followed where relevant.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed. On the basis of this drug's metabolism by CYP3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampicin, dexamethasone, St. John's Wort and certain anticonvulsivants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, isolated cases of malformations are observed in rabbits, but not in rats or mice, and are too few to be considered significant, or attributable to mifepristone.
In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit (viable ongoing pregnancy), and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultrasonographic monitoring of the pregnancy will be established.

Lactation
Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects on ability to drive and to use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

- Urogenital
  - Bleeding
    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.
  - Infection following abortion. Suspected or confirmed infections (endometritis, pelvic inflammatory disease) have been reported in less than 5% of women.
  - Very rare cases of fatal toxic shock caused by Clostridium sordellii endometritis, presenting without fever or other obvious symptoms of infection, have been reported after medical abortion with the use of 200 mg mifepristone followed by non authorised vaginal administration of misoprostol tablets for oral use. Clinicians should be aware of this potentially fatal complication (see section 4.4. – special warnings and special precautions for use).
- Gastrointestinal
  - Cramping, light or moderate (common).
  - Nausea, vomiting, diarrhoea (these gastro intestinal effects related to prostaglandin use are frequently reported).
- Rarely hypotension (0.25%)

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.
- Other systems
  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

4.9 Overdose

No case of overdose has been reported.
In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/ ANTIPROGESTOGEN : GO3 X B01.

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10 mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction-inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data is available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

The success rate is around 95 % when 600 mg mifepristone is combined with misoprostol 400 µg orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98% up to 49 days of amenorrhea and 95% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially Mifegyne followed by a prostaglandin analogue, of which:
- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

In pregnancies up to 49 days of amenorrhea, comparative studies between 200 mg and 600 mg of mifepristone in combination with 400 µg misoprostol orally cannot exclude a slightly higher risk of continuing pregnancies with the 200 mg dose.

In pregnancies up to 63 days of amenorrhea, comparative studies between 200 mg and 600 mg of mifepristone in combination with 1 mg gemeprost vaginally suggest that 200 mg mifepristone may be as effective as 600 mg mifepristone:

- Complete abortion rates with 200 mg and 600 mg were 93.8% and 94.3%, respectively, in women with < 57 days of amenorrhea (n=777. WHO 1993), and 92.4% and 91.7%, respectively, in women with 57 to 63 days of amenorrhea (n=896, WHO 2001).
- Rates of ongoing pregnancies with 200 mg and 600 mg were 0.5% and 0.3%, respectively, in women with < 57 days of amenorrhea, and 1.3% and 1.6%, respectively, in women with 57 to 63 days of amenorrhea.

Combinations of mifepristone with prostaglandin analogues other than misoprostol and gemeprost have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol. Glucocorticoid bioactivity (GBA) may be depressed for several days following a single administration of 200 mg mifepristone for termination of pregnancy. The clinical implications of this are unclear, however vomiting and nausea may be increased in susceptible women.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600 mg mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity. In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf-life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Special precautions for disposal <and other handling>

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[See Annex 1 -To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[-To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
BOX

1. NAME OF THE MEDICINAL PRODUCT

Mifegyne 200 mg tablets
Mifepristone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Mifepristone 200 mg

3. LIST OF EXCIPIENTS

[To be completed nationally]

4. PHARMACEUTICAL FORM AND CONTENTS

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral route.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

[To be completed nationally]

8. EXPIRY DATE

Exp {month/year}

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch No.
Exp {month/year}

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

{NATURE/TYPE}

1. NAME OF THE MEDICINAL PRODUCT

Mifegyne 200 mg tablets
Mifepristone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

Exp {month/year}

4. BATCH NUMBER

Batch No.

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Mifegyne 200 mg tablets
Mifepristone

Read all of this leaflet carefully before you start taking this medicine.
- *Keep this leaflet .You need to read it again.*
- *If you have any further questions, ask your doctor .*
- *This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.*
- *If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.*

In this leaflet:
1. What Mifegyne is and what it is used for
2. Before you take Mifegyne
3. How to take Mifegyne
4. Possible side effects
5. How to store Mifegyne
6. Further information

1. WHAT MIFEGYNE IS AND WHAT IS IT USED FOR

Mifegyne is an anti-hormone that acts by blocking the effects of progesterone, a hormone which is needed for pregnancy to continue. Mifegyne can therefore cause termination of pregnancy. It can also be used to soften and open the entrance (the cervix) to the womb (uterus).

Mifegyne is recommended for the following indications:
1) For the medical termination of a pregnancy:
- no later than 63 days after the first day of your last period,
- in combination with another treatment called prostaglandin (a substance that increases contraction of the womb) which you take 36 to 48 hours after taking Mifegyne.
2) For softening and opening the cervix before surgical termination of pregnancy during the first trimester.
3) As pre-treatment before giving prostaglandins for termination of pregnancy for medical reasons beyond 3 months gestation.
4) To induce labour in cases where the fetus has died in the womb and where it is not possible to use other medical treatments (prostaglandin or oxytocin).

2. BEFORE YOU TAKE MIFEGYNE

DO NOT TAKE MIFEGYNE:

• **In all cases**,
- if you are allergic (hypersensitive) to the active substance mifepristone or any of the other ingredients of Mifegyne,
- if you suffer from adrenal failure,
- if you suffer from severe asthma, which cannot be adequately treated with medication,
- if you have hereditary porphyria.

• **In addition,**
For termination of pregnancy up to 63 days amenorrhoea:
- if your pregnancy has not been confirmed by a biological test or an ultrasound scan,

- if the first day of your last period was more than 63 days ago,
- if your doctor suspects an ectopic pregnancy (the egg is implanted outside the womb),
- because of the need to prescribe a prostaglandin in association with Mifegyne, you must not take this treatment if you are allergic to prostaglandins.

For softening and opening the cervix before surgical termination of pregnancy:
- if the pregnancy has not been confirmed by a biological test or ultrasound scan,
- if your doctor suspects an ectopic pregnancy.
- if the first day of your last period was 84 days ago and more.

For termination of pregnancy beyond 3 months gestation:
- if prostaglandins have to be used to complete the action of Mifegyne, please also refer to the product information of that medicine,
- because of the need to prescribe a prostaglandin in association with Mifegyne, you must not take this treatment if you are allergic to prostaglandins.

For inducing labour when the foetus has died in the womb.

Take special care with Mifegyne

In some other circumstances the treatment may also be unsuitable to you so please tell your doctor if:
- you have a heart complaint,
- you have a risk factors for heart diseases, such as high blood pressure or high blood cholesterol levels (increased fat content in your blood),
- you suffer from asthma,
- you suffer from an illness that may affect the clotting of your blood,
- you have liver or kidney disease,
- you are anaemic or otherwise malnourished.

The doctor will then be able to discuss with you if you are able to have the treatment.
You can have prolonged and/or heavy vaginal bleeding (an average of about 12 days or more after Mifegyne intake). The presence of those bleedings are not related to the success of the method.

Taking other medecines

Medecines containing the following active substances may interfere with the action of Mifegyne:
- corticosteroids (used in the treatment of asthma or other inflammation treatments)
- ketoconazole, itraconazole (used in antifungal treatment)
- erythromycin, rifampicin (antibiotics)
- St John's Wort (natural remedy used in the treatment of mild depression)
- phenytoin, phenobarbital, carbamazepine (used in the treatment of seizures; epilepsia)

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Mifegyne with food and drink

Grape fruit juice should not be taken when you are treated with Mifegyne.

Pregnancy and breast feeding

Because Mifegyne may pass into breast milk and be taken in by your baby, you should stop breast feeding once you have taken the treatment.
There is little information on the risks to the unborn baby. If the pregnancy continues and you decide to keep it, discuss this with your doctor who will arrange careful pre-natal monitoring and ultrasound examinations.
It is recommended that you avoid getting pregnancy again before your next menstrual period after taking Mifegyne.

Important information about some of the ingredients of Mifegyne

[To be completed nationally]

3. HOW TO TAKE MIFEGYNE

1) Medical termination of a developing intra-uterine pregnancy

Mifegyne is taken as a single dose of 3 tablets each containing 200mg mifepristone. The tablets should be swallowed with some water in the presence of a doctor or a member of his/her medical staff.
The prostaglandin (misoprostol 400 micrograms) is either given as tablets which should be swallowed with water or as a vaginal pessary (gemeprost 1 mg). The prostaglandin is taken as a single dose 36 – 48 hours after taking the Mifegyne.
This method involves your active participation and you should therefore be aware that:
- You need to take the second medicament (which contains prostaglandin) to ensure the treatment is effective.
- You need to attend a check-up consultation (3rd consultation) within 14 - 21 days of taking Mifegyne in order to check that your pregnancy has been completely expelled and you are well.
- The method of medical pregnancy termination using the combination of Mifegyne and prostaglandin is not 100 % effective. The average success rate is 95% and you may therefore require a surgical procedure to complete the treatment.

For pregnancies that have occurred with a contraceptive coil in place, the coil will be removed prior to administering Mifegyne.

The schedule below will be followed.
After the Mifegyne has been administered, you return home. Uterine bleeding usually starts 1 to 2 days after taking Mifegyne.
In rare cases, an expulsion can occur before you take the prostaglandin. It is essential that you are checked to confirm that a complete evacuation has occurred and you must return to the centre for this.
Two days later the prostaglandin will be administered. You should stay at rest for 3 hours after having the prostaglandin. The pregnancy may be expelled within a few hours of prostaglandin administration or during the next few days. The bleeding lasts in average 12 days or more. In case of heavy and prolonged bleeding, the patient should contact the doctor immediately in order to re-schedule an earlier appointment.
You must return to the centre for the check-up consultation within 14 - 21 days after taking Mifegyne. If pregnancy continues or expulsion is incomplete, you will be offered another method for terminating the pregnancy.
It is recommended that you do not travel too far away from your prescribing centre until this date.
In an emergency or if you are worried for any reason, you can telephone your centre or go back to it before the date fixed for the next consultation. You will be given the telephone number to call for emergencies or for any problem.

Alternatively, 200 mg of mifepristone can also be used in a single oral dose. This oral dose should be followed 36 to 48 hours later, by the administration of the prostaglandin analogue gemeprost 1 mg in the vagina.

2) For softening and opening the cervix before surgical termination of pregnancy:

Mifegyne is taken as a single dose of one tablet containing 200mg mifepristone. The tablet should be swallowed with some water in the presence of a doctor or a member of his/her medical staff.
- After Mifegyne administration, you return home with an appointment 36 to 48 hours later for the surgical procedure. Your doctor will explain the procedure to you. It is possible that you will experience bleeding after taking Mifegyne, before the surgery.

In rare cases, expulsion can also occur before surgery. It is essential that you are checked to confirm that a complete evacuation has occurred and you must return to the centre for this.
- You will be given a telephone number to call for emergencies.
- You must return to the centre selected for the surgery. You will rest for a few hours after the surgery then return home.

3) For termination of pregnancy beyond first three months of gestation:
Mifegyne is taken as a single dose of 3 tablets each containing 200mg mifepristone. The tablets should be swallowed with some water in the presence of a doctor or a member of his/her medical staff. You will be given an appointment for admission to treatment centre 36 to 48 hours later (2 days) to receive the prostaglandin which may need to be given several times at regular intervals until the termination is complete.

4) For inducing labour when pregnancy has been interrupted (intra-uterine foetal death).
3 tablets of Mifegyne are taken each day for two days. The tablets should be swallowed with some water.

In all cases
The use of Mifegyne requires that measures are taken to prevent Rhesus factor sensitisation *(if you are Rhesus negative)* along with the general measures taken during any pregnancy termination.
It is possible for you to become pregnant again immediately after the pregnancy termination is complete.
As some effects of Mifegyne may still be present, it is recommended that you avoid getting pregnant again before your next menstrual period after taking Mifegyne.

If you take more Mifegyne than you should
As you will be supervised during administration of the treatment it is unlikely that you will take more that you should.

If you forget to take Mifegyne
If you forget to take any part of the treatment, it is likely that the method will not be fully effective. Talk with your doctor if you forgot to take the treatment.

If you have any further questions on the use of this product, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Mifegyne can cause side effects, although not everybody gets them.

Very common (occur among more than 1 in 10 patients): heavy bleeding, uterine contractions or cramping in the hours following prostaglandin intake.

Common (occur among more than 1 in 100 patients but less than 1 in 10 patients): Infection following abortion, effects related to prostaglandin use such as nausea, vomiting or diarrhoea.

Uncommon (occur among more than 1 in 1000 patients but less than 1 in 100 patients): skin rashes, headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever. Blood pressure fall have also been observed.

Very rare (occur among less than 1 in 10000 patients): cases of fatal toxic shock caused by infection by *Clostridium sordellii endometritis*, presenting without fever or other obvious symptoms of infection.

Single cases of side effects observed are: hives and skin disorders sometimes serious.

In a very small number of women, especially those who have had an operation on the womb or have had a baby by cesarean delivery, there is a risk that the uterus or womb may split or rupture.

Other side effects are gastrointestinal cramping, light or moderate.

Pregnancy
If the pregnancy continues and you decide to keep it, discuss this with your doctor who will arrange careful pre-natal monitoring and repeated ultrasound examinations.

5. HOW TO STORE MIFEGYNE

Keep out of reach and out of sight of children.
Do not use after the expiry date indicated on the box.
Do not use if the box or the blisters show signs of damage.
[To be completed nationally]

6. FURTHER INFORMATION

What Mifegyne contains
The active ingredient is mifepristone.
The other ingredient(s) is (are)
[To be completed nationally]

What MIFEGYNE looks like and contents of the pack.
[To be completed nationally]

Marketing Authorisation Holder and Manufacturer
[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following name: MIFEGYNE.
This leaflet was last approved in {date} [To be completed nationally]