- Urogenital

  - Bleeding

    Bleeding occurs in almost all women and increases with the age of pregnancy at the time of termination.

    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.

  - Uterine rupture has been uncommonly reported after prostaglandin intake for induction of second trimester termination of pregnancy of labour induction for fetal death in utero during the third trimester.

    The reports occurred particularly in multiparous women or in women with a cesarean section scar.

- Gastrointestinal

  Nausea, vomiting, diarrhea, very common after prostaglandin intake.

- Cardiovascular

  Uncommon hypotension (0.25%).

- Hypersensitivity and skin

  Uncommon skin rashes (0.2%): Single cases of urticaria, of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.

- Other systems

  Rare cases of headaches, malaise, common vagal symptoms (hot flushes, dizziness, chills), and uncommon fever have been reported.

4.9 Overdose

Dose-ranging studies have shown that administration of single doses of mifepristone up to 2 g caused no unwanted reaction.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Any suggestion of acute intoxication, therefore, requires treatment in a specific environment, and if relevant with dexamethasone administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION / ANTIPROGESTOGEN (G03 X B01: Urogenital System and Sex Hormones).

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 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 prostaglandins.

During the first trimester, it allows the dilatation and opening of the cervix uteri.

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

During the termination of pregnancy for medical reasons, 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 requirements.

When used for labour induction in fetal 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 prostaglandins or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. 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.

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 the peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects). The absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein, to which binding is saturable.

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.

Two primary metabolic pathways have been demonstrated: N-Demethylation and terminal hydroxylation of the 17-propynyl chain.

After administration of the same labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

Studies on the reproductive system have shown that mifepristone administration induced rare fetal anomalies in one species (rabbits) (see section Pregnancy and Lactation). No deleterious effect occurred in rats, mice and monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous colloidal silica, maize starch, povidone, microcrystalline cellulose, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf-life

APPEARS THIS WAY
ON ORIGINAL

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Blister pack (PVC and Aluminium foil and carton) containing 3 tablets.

6.6 Instructions for Use/Handling

The treatment procedure should be fully explained and completely understood by the patient.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTORISATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF THE TEXT

September 1998.

NEW FOREIGN MARKETING INFORMATION (Cont.)

Mifegyne® (Mifepristone)

International Regulatory Approval Status
(November 1998)

MIFEGYNE®

REGISTRATION STATUS AS OF NOVEMBER 1998

COUNTRY	DOSAGE PER TABLET	DATE OF APPROVAL	DATE OF LAUNCH	DATE OF TRANSFER OF MARKETING AUTHORIZATION	INDICATIONS (and POSOLOGY)
FRANCE	200 mg	December 28, 1988 July 17, 1992 Q4, 1998	September 1989	8/8/97 CIP N° 556 473.0	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 49 days amenorrhea (600 mg single dose) • Preparation for the prostaglandin action in therapeutic pregnancy Termination (600 mg single dose) • Fœtal death in utero (600 mg x 2 days) • Softening and dilatation of the cervix uteri prior to voluntary pregnancy termination by vacuum aspiration during the first trimester (200 mg single dose)
U.K.	200 mg	July 1st,1991 August 4, 1995	July 1991	24/09/97 PL 16152/0001	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600 mg single dose) • Softening and dilatation of the cervix uteri prior to mechanical cervical dilatation for pregnancy termination (600 mg single dose) • Termination of pregnancy between 13 and 20 weeks gestation in combination with gemeprost (600 mg single dose)
SWEDEN	200 mg	September 4, 1992 August 2, 1995	October 1992	1/10/97 ASP 91-0246 ASP 95-0005	• Medical alternative to surgical termination of intra-uterine pregnancy of up to 63 days amenorrhea (600 mg single dose) • Termination of pregnancy in the second trimester (600 mg single dose) • Same indications as for 200 mg tablets
U.S.A.	200 mg	Approvable letter September 18,1996			• Medical termination of intra-uterine pregnancy through 49 days duration of pregnancy

NEW FOREIGN MARKETING INFORMATION (Cont.)

International Regulatory Approval Status (Cont.)

Mifepristone was also approved on July 6, 1999 under the mutual recognition procedure of the European Union in eight additional countries. One of these countries is Germany. A summary of a press release which appeared in a local newspaper is attached on the next page.

LITERATURE UPDATE

Overview of Literature

Overview of Literature

A total of 61 clinical studies published between 1996 and 1999 were reviewed. These studies used mifepristone in different clinical conditions and for variable time intervals. In those studies on early pregnancy termination, the incidence of side effects observed was similar to that reported in previous submissions. This report summarizes side effects reported in later gestations as well as in studies unrelated to pregnancy termination. Full details are available in copies of the reprints that are included in this section following the bibliography.

Phillips *et al.* (1996) reported on a 26-year-old woman who requested termination of her pregnancy. She estimated that she was about 14 weeks pregnant. She had no history of cervical or uterine surgery. Examination of the abdomen suggested a more advanced pregnancy of 18 weeks. She was given mifepristone (200 mg) followed 48 hours later by misoprostol (600 mg) vaginally. A further dose of the latter was administered vaginally 6 hours later and 4 hours later painful uterine contractions commenced. After the fetus was delivered, severe abdominal pain occurred and necessitated intravenous narcotic analgesia. At this stage she appeared pale and peripherally shut down. Her pulse was 88/min, blood pressure 100/60 mmHg. Emergency manual removal of the placenta was performed under general anesthesia. Once removed the uterine cavity was checked digitally and it was evident that there was a large defect in the uterine wall that was surgically repaired. This is the first case of uterine rupture following oral mifepristone and intravaginal misoprostol. There are two previously published case reports of uterine rupture associated with mifepristone in combination with gemeprost. One is a third trimester abortion (Bouluf et al.Gynaecol Obstet Invest 1993; 36: 87 - 90 and the other is a second trimester termination of pregnancy (Norman JE. Br J Obstet Gynaecol 1995; 102: 332-333). An additional case is listed below.

The UK Multicenter Study Group (1997) administered Mifepristone 600 mg and Vaginal gemeprost in an open multicenter study conducted in 267 women for mid trimester induction of abortion (up to 24 weeks). Vomiting, pelvic pain, and nausea were the most frequently reported adverse events. Two patients required transfusion and one patient with a uterine scar from a previous caesarian section suffered a ruptured uterus and required hysterectomy.

Gemzell Danielsson, Swahn, Welstlund *et al.* (1997) administered low daily doses of mifepristone (0.1 or 0.5 mg daily for 3 months). There were 5 subjects in each group. With the higher dose, 2 patients complained of acne during the first treatment month. In these subjects there were no problems during the following treatment cycles. No other side effects were observed.

Marions *et al.* (1998) administered mifepristone (5mg) once weekly starting on cycle day 2 for a total of 6 months to 18 women. This was their only contraceptive method. The treatment resulted in a significant decrease in pregnancy rate without affecting menstrual cycle or ovulation. Four patients reported pelvic pain during the first treatment month.

In the study of Kettel *et al.* (1998), 6 patients with endometriosis were given mifepristone in a dose of 5mg daily for 6 months. One patient experienced a mild increase in hepatic transaminases, two patients experienced hot flushes that resolved at the end of the third treatment month and one patient experienced depression for 6 weeks after treatment started.

Heikinheimo *et al.* (1998) administered mifepristone (200mg) daily to 7 patients with inoperable meningioma. TSH values increased significantly ($P < .005$, one-way ANOVA), with the most pronounced increase evident during the first 3 months of mifepristone treatment. Despite these changes, concentrations of TSH remained within the normal range throughout the treatment period. There were no significant changes in serum T4, fT4, T3 or prolactin; however, a transient decrease in serum T4 was noted at 2 to 3 months. These results indicate that chronic mifepristone administration induces biochemical hypothyroidism.

A total of 28 postmenopausal women with metastatic breast carcinoma were treated with mifepristone 200mg daily (Perrault *et al*, 1996). Adverse effects noted included lethargy, anorexia, nausea, and hot flashes. These were common but seldom severe. Two patients experienced a severe skin rash that resolved when mifepristone was interrupted. There was no recurrence of the rash once drug administration resumed. Mifepristone did not produce any hematologic toxicity. Mild elevations of AST were observed in some patients, and one developed significant reversible hypokalemia while on therapy. Seventeen patients had serial TSH measures obtained, and all showed an increase in TSH, although this was above the upper limit of normal in only six patients. Of these six, two had been on replacement thyroid hormone at baseline, and two additional patients were started on replacement therapy whilst on the study.

Bertagna *et al.* (1997) administered mifepristone (200 mg/day) or placebo between 0800-0900h for eight days to 10 normal males. Blood glucose was slightly higher at the end of treatment (5.0 ± 0.2 vs. 4.7 ± 0.1 mmo/L; $p<.04$).

Jobin *et al.* (1996) administered mifepristone (600mg) the night before ingestion of a standardized meal to 12 healthy male volunteers. Plasma glucose and insulin concentrations were also measured at regular intervals. Baseline glucose concentrations were similar but were significantly higher 90 minutes postprandial with mifepristone: (5.3 ± 1.7 mmol/L vs 3.7 ± 0.8 mmol/L for placebo). Plasma insulin was similar at baseline but it was also significantly higher at 90 minutes postprandial after mifepristone (347 ± 143 vs 241 ± 73 pmol/L for mifepristone and placebo, respectively). This study showed that acute inhibition of glucocorticoid action induced a mild deterioration of glucose tolerance.

LITERATURE UPDATE (Cont.)

Bibliography and Reprints of Clinical Literature

LITERATURE UPDATE - CLINICAL

The present update to the NDA bibliography was generated by a Medline search using the following key words (English only): mifepristone, RU486, abortifacient, progesterone antagonist and human from mid 1996 through June 18, 1999. (This bibliography covers the period following the first Safety Update Report submitted on June 20, 1996.)

The bibliography generated by this strategy includes published articles on clinical investigatons on mifepristone. A list of these references is presented below and copies of reprints are attached. The reprints of these articles are organized alphabetically by author.

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