SUMMARY OF PRODUCT

1. PRODUCT NAME

ENZAPROST F

Solution for injection

2. Qualitative A QUANTITATIVE COMPOSITION

Dinoprostum 5.0 mg in 1 ml of solution for injection.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection
A clear, colorless to pale greenish-yellow solution, practically free of visible particles.

4. CLINICAL DATA

4.1 Therapeutic indications

- Therapeutic abortion when pregnancy pathologies: early death of the fetus in the second trimester, severe fetal malformations (anencephaly, hydrocephalus, Amelie) diagnosed by ultrasound or other method of prenatal diagnosis
- Induction birth in the following cases: intrauterine fetal death (late fetal death, termination of pregnancy for fetal developmental defects, premature rupture of membranes and primarily poor uterine activity, delivery of placenta).

4.2 Dosage and method of administration

Dosage

Intraamniotickou injection can be administered transabdominally or through the vaginal vault.

Premedication:
The suppression of side effects and pain can use the following combinations:

	First [Mg]	2nd [Mg]	3rd [Mg]	4th [Mg]
Pethidine	100.00	100.00	100.00	50.00
Promethazine HCL	-	50.00	50.00	-
Atropine	0.05		0.50	0.25
Diazepam	10.00		-	-

It is recommended to use pethidine and atropine. The selected combination is administered intravenously immediately prior to application of Enzaprost F.

Transabdominál her application:
Before the surgery must be emptied bladder. After disinfecting the skin at the injection site amniocentesis performed under local anesthetic, in the midline of the abdomen, 3-4 fingers above the pubic arch. Aspiration of amniotic fluid into the syringe should make sure that the needle is actually in the amniotic cavity.
Subsequently, injected with 25 mg of F Enzaprost into the amniotic cavity. If necessary, the injection can be for 8-12 hours again, and using a plastic cannula left in the puncture after amniocentesis. (If blood appears in the aspiration of amniotic fluid or blood, injection omission.) Before the treatment, it is necessary to locate the placenta by ultrasound.

Appli cations through the vaginal vault:
Bladder must be emptied. Vagina and vaginal mucosa must be disinfected. Vaginal portion of the cervix is fixed using clamps.
To amniotic cavity is usually penetrates through the rear, in some cases through the front vaginal vault. Uploading a few ml of amniotic fluid can check the correct needle position. If the amniotic fluid clear, administered 25 mg of Enzaprost F. This procedure can be repeated.
Uterine action must be constantly checked by palpation, tokograficky and occasional examination of the cervix. In case of failure may be administered a second injection of Enzaprost F for 8 to 12 hours and, if necessary, add it to an infusion of oxytocin. Unless within 12 hours to have an abortion, it is necessary to tighten pregnant (pulse, temperature, leukocyte count).

Both method can only be used for specialized gynecological and obstetrical wards, where there are intensive care unit.

To achieve a continuous level of the medicinal product in the blood for pathological pregnancies particularly recommends the use of an infusion pump.

After the termination of pregnancy is necessary to verify the complete evacuation because any retention can lead to the need for surgery.
If is used to terminate the pregnancy dinoprost, the process must be completely finished, because dinoprost effect on the fetus is not yet understood.

4.3 Contraindication

Allergy or hypersensitivity reactions to dinoprost or other haemorrhagics including uterotonics history.
Bronchial asthma (bronchial asthma or history), chronic obstructive pulmonary disease, pulmonary disease active phase.
Active and dormancy ulcerative colitis, Crohn's disease, thyrotoxicosis, sickle cell anemia, glaucoma, acute infection.
Acute inflammation pelvic or abdominal (eg. chorioamnionitis manifest, which induces clinically apparent contraction of the uterus, which should be avoided), rupture of the membranes (increased risk of intravascular absorption dinoprost).
Significant kefalopelvická disproportion abnormal fetus, hypertension (160/100 mm Hg or more).

4.4 Special warnings and precautions for use

In these cases it is necessary to consider the risk-benefit ratio:

Cardiovascular disorders: Heart disease with acute symptoms of existing cardiovascular disease (or a history thereof) existing hypertension or hypotension (or these diseases
history).

Disorders of the central nervous system: Epilepsy (or a history of epilepsy).

*Endocrine and metabolic disorders*Diabetes mellitus / or history of diabetes mellitus).

Gastrointestinal disorders: Jaundice (or a history of jaundice) or acute liver disease.

*Genitourinary disturbance*Acute renal disease (kidney disease or a history), pre-eclampsia, cervical stenosis, leiomyoma and myoma, earlier surgery on the uterus (risk of uterine rupture), multiple pregnancy.

*Others*Anemia (or anemia in history).

Unintentional dinoprost absorption may cause nausea, vomiting, bronchoconstriction, peripheral vasoconstriction, fainting, weakness, hypertension, and a feeling of panic. Given that Enzaprost F is rapidly metabolized, these effects are transient (lasting 15 to 30 minutes), and are usually not clinically significant.
Before induction of labor should be carefully evaluated potential kefalopelvická disproportion. During the infusion should be carefully monitored uterine activity, fetal condition, the development of cervical dilatation in order to identify any adverse reactions, for example. Hypertonus uterus, persistent uterine contractions, fetal distress.
Patients who have a history of hypertonic or tetanic contractions of the uterus should be throughout their labor for activity of the uterus and the fetus. When hypertonic contractions of the uterine muscles to keep in mind the possibility of uterine rupture.

Patients over 35 years, patients with problems during pregnancy and in patients after 40 weeks of pregnancy should be dinoprost administered to induce labor with great caution because of an increased risk of disseminated intravascular coagulation (DIC).

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of oxytocin and ergometrine enhances the effect of Enzaprost F and increases the risk of side effects.

4.6 Pregnancy and lactation

Injection Enzaprost of F are used for abortions (see section 4.1).
If is used to terminate the pregnancy dinoprost, the process must be completely finished, because dinoprost effect on the fetus is not yet understood.
In animal studies, following administration of high doses of prostaglandins E and F was observed proliferation of bone tissue. During the clinical application of bone tissue proliferation was also reported in long term treatment by prostaglandin E1.
Short Treatment dinoprost similar changes in the fetus probably does not.

4.7 Effects on ability to drive and use machines

Is not relevant.

4.8 Side effects

Side effects are sorted by frequency as follows: very common (≥1 / 10); common (≥1 / 100 to <1/10); uncommon (≥1 / 1,000 to <1/100); rare (≥1 / 10,000 to <1/1000); very rare (<1/10000); not known (from the available data can not be determined).

Examination
Uncommon: Increased number of white blood cells.

Cardiac disorders:
Uncommon: Anaphylactic shock, peripheral vasoconstriction, tachycardia, AV block second degree, substernal pressure or pain, chest pain.

Nervous system disorders
Uncommon: Headache, somnolence, transpiration, anxiety, diplopia, paresthesia.

Eye disorders
Rare: Burning eyes.

Respiratory, thoracic and mediastinal disorders
Uncommon: Persistent cough. Rare:
bronchoconstriction.

Gastrointestinal disorders
Very rare: Nausea, vomiting, diarrhea, stomach cramps or pain.
Rare: Intensive and constant abdominal or epigastric pain, paralytic ileus.

Renal and urinary disorders
Uncommon: Dysuria, hematuria, urinary retention.

Musculoskeletal system and connective tissue
Rare: Pain leg, back or shoulder.

General disorders and administration site
Uncommon: Tremor, cold or rapid breathing, transient fever, redness, unusual thirst. Inflammation and pain at the injection site.

Reproductive system and breast
Uncommon: Pain accompanying uterine abortion, increased tone of the
uterus. Rare: breast swelling due to congestion, burning breasts.

Blood and lymphatic system
In patients in whom the birth was induced pharmacologically using either oxytocin or dinoprost, have a greater risk of DIC (see section 4.4)

HAsena suspected adverse Prior inky
Reporting suspected adverse effects after registration of a product is important. Allows you to continue watching the benefit-risk ratio of the medicinal product. We are asking healthcare professionals to report suspected adverse reactions to the following address:
State Institute for Drug Control
Šrobárova 48
100 41 Praha 10
Web site: www.sukl.cz/nahlasit-nezadouci-ucinek

4.9 Overdose

Clinical signs of overdose:
Nausea, vomiting and diarrhea are significantly more intense than normal dose administration.

Treatment:
Specific Treatment: if necessary, surgical rupture of the membranes (reservoir medication). Supportive therapy: intravenous fluid replacement.

Is important to make sure that the application technique was correct.

When ouster hydatiformní moths may be a leak of prostaglandin into the systemic circulation, which causes these reactions are: muscle stiffness and hypotension, vomiting and suprapubic pain, fever and flushing may develop a deep and significant bradycardia, hypotension. In this case, the product should be discontinued and symptomatic treatment.

5. Pharmacological FEATURES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Uterotonicum, ATC code: G02AD01

Naturally occurring prostaglandins are divided into subgroups (prostaglandin A, B, C, D, etc.) by substitution in the cyclopentane ring. Prostaglandins are not adhered to the tissue, but are newly synthesized by microsomal enzymes (e.g. cyclooxygenase) present from arachidonic acid in response to mechanical stimulation or bacterial.

In obstetrics are three emerging importance prostanoids [(prostaglandin E1: alprostadil, prostaglandin E2: dinoprostone and prostaglandin F2 alpha: dinoprost (Enzaprost F)], which induces myometrial contractions and contribute to cervical ripening.
Prostaglandin F2 is in fact a reduced form of prostaglandin E2 (in vivo are formed in connection with the spontaneous conversion of prostaglandin E2).
Prostaglandins occur in all organs and tissues.
During pregnancy , the synthesis of prostaglandins in the amnion, chorion and placenta increases, which leads to significantly higher levels of prostaglandin amnionické fluid and in maternal blood.

Mechanism of action
Dinoprostone and dinoprost (Enzaprost F) activates phospholipase C, thus increasing the permeability of cell membranes for calcium. As a result of elevated intracellular calcium leads to myometrial contractions. These substances are also involved in cervical ripening. Cells smooth muscles have specific receptors for prostaglandin E2 and prostaglandin F2 alpha, and these prostaglandins affect specific membrane receptors on target cells.
Prostaglandins outside It also improves signal transmission in the myometrium induction of cell junctions and induces the formation and increase in the number of oxytocin receptors in the uterus.

Other action
Local administration prostaglandin leads to obvious multifocal loss of connective tissue with the presence of "active" fibroblast (finely granular cytoplasm, mitochondria with enlarged vacuoles and increased number of vacuoles or vesicular system to the periphery cells). At the same time doubling the activity of collagenase, elastase activity is increased about 7-fold and was observed a significant increase in the level of hyaluronidase. These factors are involved in cervical ripening. .
Collagenase produced mainly by neutrophilic granulocytes, which, when administered prostaglandin accumulates in large amounts in the cervical stroma (like during labor at term).
Prostaglandins also induce increased activity of NK cells, which contribute to induction of labor and habitual abortion.
Prostaglandins Thus on the one hand causing cervical ripening and on the other hand, induction of labor. Both effects are used in therapy.

Enzaprost F is prostaglandin (prostaglandin F2 alpha), which causes uterine contractions for termination of pregnancy after 15 weeks of gestation. After application to the bag causes amniotického during 15-30 minutes hypertonus, which gradually (over one hour.) Change to the regular synchronous contraction (greater than 100 mmHg) including smooth muscle wall of the uterus. Studies concerning its influence on hormone levels indicate that causes a decrease in the levels of progesterone and estradiol, probably through direct effects on placental steroidogenesis. These changes progesterone and estradiol are small and may relate to the start of labor.

Intraamniotická injection was effective in treating severe postpartum haemorrhage.
Enzaprost F induced transient depression after a slight increase in blood pressure. The cause of the rise in blood pressure, vasoconstriction, while his temporary reduction is most likely explained by the effect of vasodilating substance itself.

5.2 Pharmacokinetic Properties

Absorption in the body
Enzaprost enters the blood stream from amniotického bag - is almost completely metabolized (90%) in a single passage through the liver and lungs. The time to maximum concentration is 6-10 hours after a single dose of 40 mg intraamnionální. Cmax is 3-7 ng per ml dinoprost.

Biotransformation
The enzymatic oxidation occurs primarily in the lungs and the liver of the mother. Dinoprost is cleaved 15-OH dehydrogenase; resulting intermediate in a ketone, which is then oxidized to 2,3 nidor 6-keto prostaglandin F1 alpha.

Elimination from the organism
Dinoprost is excreted as metabolites in the kidneys (5% is excreted in faeces). Half
in amniotic fluid is 3-6 hours (determined by immunoassay), in contrast to the peripheral plasma following IV administration, which takes less than 1 minute.

5.3 Preclinical safety

In experiments on animals have not shown toxic or mutagenic substances.

Acute toxicity

	iv application		IM application	
LD_{50} mg / kg	male	female	male	female
mouse	9.78	26.52	60.54	169.0
rat	20.0		-	

Cardiovascular and other side effects of Enzaprost F were observed in cats after iv applying increasing doses.
Turns that doses greater than 1 mg / kg cause respiratory paralysis and cardiac arrest with fatal outcome.

Subacute toxicity
After 4 weeks of intraperitoneal administration of Enzaprost F rats at doses of 0.3 mg / kg showed no toxic damage. In these experiments, dogs were also observed no changes in terms of clinical symptoms and laboratory values morphological structure bodies.

Teratogenicity / Fertility
In mice, there was no teratogenic effect of Enzaprost F. Administration of Enzaprost F at a dose of 1 mg / kg sc had no effect on fertility in female rabbits.

Preclinical Data on clinical use are not available (see section 4.6).

6. PHARMACEUTICAL SPECIFICATIONS

6.1 List excipients

Trihydrate sodium acetate, water for injections

6.2 Incompatibilities

None known.

6.3 Time usability

3 years

6.4 Special precautions for storage

Keep at 5 -15 ° C. The ampoules in the outer carton in order to protect from light.

6.5 Kind and contents of container

OPC breakaway vial Clear glass, plastic harvesting, packing box size: 5 x 1

ml.

6.6 Instruction for use and handling

Local administration (intraamniotic).

No special requirements for disposal.

Any unused product or waste material should be disposed of in accordance with local requirements.