PATIENT INFORMATION LEAFLET

UTESEL 0.2 mg / 1 mL I.M./I.V. ampoule containing solution for injection
Sterile
It is administered intramuscularly and intravenously

Drug substance: Each 1 mL ampoule contains 0.2 mg methylergobacin maleat.
Excipients: Thiourea, sodium chloride, tartaric acid and water for injection.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use high or low doses other than the recommended dosage.*

What is in this leaflet:

Headings are included.

1. What UTESEL is and what it is used for?

- UTESEL is a colorless solution administered intramuscularly and is included in a group of drugs (prostaglandins / oxytoics) that provide uterine contraction.
- UTESEL is packed in 1 mL amber glass ampoule. Each box contains 3 or 50 ampoules.
- UTESEL reduces the incomplete excretion of the uterus at the second stage of birth, incomplete abortion, after the arrival of the baby's partner and the emergence of the anterior shoulder, in the prevention and treatment of uterine bleeding due to the inability to contract and return to the state before pregnancy, after the arrival of the baby's partner and the emergence of the forearm (discharge from the uterus).

2. What you need to know before you use UTESEL

Your doctor may want to monitor your blood pressure, pulse rate and your uterus's response to treatment by connecting you to a monitor to monitor whether or not UTESEL treatment is adequate.

DO NOT USE UTESEL
If;

- You have high blood pressure
- You are pregnant
- You are hypersensitive to methylergobacin maleat or to any of the ingredients contained in UTESEL,
- Pregnancy poisoning (preeclampsia, eclampsia, can be seen in pregnancy, protein excretion in urine, high blood pressure, edema, seizures), if you have an infection such as puerperal fever, birth to create or dangerous spontaneous miscarriage
- Drugs used to treat AIDS (eg. ritonavir, indinavir, nelfinavir, delavirdin), drugs used to treat fungi called the azole group (eg. Ketaconazole, itraconazole, variconazole) or an antibiotic called the macrolide group (e.g. erythromycin, trolleandomycin, claritromycin) if using drugs

UTESEL should not be used.

USE UTESEL CAREFULLY in the following cases
If;

- You have cardiovascular diseases
- You have an obstructive vascular disease
- You have kidney and liver diseases
- You have any of your coronary artery disease (narrowing of the heart vessels due to arteriosclerosis) or risk factors that may cause coronary artery disease (for example, if you smoke, if you are overweight, if you have diabetes, if you have high cholesterol)

If these warnings are valid for you, even at any time in the past, please consult your doctor.

Use of UTESEL with food and beverage
There is no known interaction with food and beverages in terms of administration method.

Pregnancy
Consult your doctor or your pharmacist before using the drug.

UTESEL should not be used during pregnancy.

If you notice that you are pregnant during your treatment, consult your doctor or pharmacist immediately.

Breast-feeding

Consult your doctor or your pharmacist before using the drug.

UTESEL should not be used during breastfeeding.

UTESEL has been reported to reduce breast milk secretion and pass into breast milk. There are some reports of poisoning in infants who are breastfed after breastfeeding women use the drug for a few days. One or more of the following symptoms have been observed and disappeared with discontinuation of the drug; increased blood pressure, bradycardia (slow pulse) or tachycardia (rapid pulse), vomiting, diarrhea, restlessness, muscle cramps. UTESEL is not recommended for breastfeeding due to the possibility of side effects and reduced milk secretion for the child.

After breastfeeding, at least 12 hours should be waited for breastfeeding.

Driving and using machines
No adverse effects on the ability to drive and use machines have been reported. However, it is not recommended to use tools and machinery during UTESEL use due to the possibility of causing dizziness and seizures.

Important information about some of the excipients contained in UTESEL
UTESEL contains less than 23 mg sodium per 1 mL. No negative effects due to sodium are expected.

Use with other medicines

Other types of drugs that cause narrowing of the vessels and drugs that provide regional numbness (anesthetics) may also contain the same type of substances as UTESEL.

Medicines called beta-blockers used in diseases such as high blood pressure, chest pain, heart failure, palpitations or heart rhythm disorders, migraines (eg propranolol), medicines that may reduce the effect of UTESEL in the body (eg nevirapine, rifampicin),

Medicines that can increase the side effects of UTESEL; antibiotics called macrolide group (eg erythromycin, troleandomycin, clarithromycin), medicines used to treat AIDS (e.g. ritonavir, indinavir, nelfinavir, delavirdin) or medicines used in fungal treatment (eg ketaconazole, itraconazole, varicoconazole),

Your doctor will adjust the amount of UTESEL you will be using if you are using medications (eg glyceryl trinitrate) to prevent or reduce the frequency of chest pain (angina) caused by narrowing / occlusion of the vessels that supply the heart.

If you are currently using any prescription or non-prescription medication, or if you have used it recently, please inform your doctor or pharmacist about them.

3. How to use UTESEL

Instructions for appropriate use and dose / administration frequency:
Your physician will determine the dose of your drug product and administer it to you depending on your illness.

Route and method of administration:
UTESEL is administered into your muscle by your doctor or nurse.
If your doctor approves, it can be administered into vein in very special cases and under certain conditions. Close monitoring is required during such an administration.

Various age groups:

Use in children:
The safety and effectiveness of UTESEL on children has not been adequately studied.

Use in the elderly:
There are no clinical trials with sufficient numbers of patients aged 65 years or older for the safety and efficacy of UTESEL for the elderly. Since elderly patients may have decreased liver, kidney and heart functions, treatment should be started from the lowest dose range.

Special conditions of use:
Renal/Hepatic failure:

It should not be used in kidney and liver diseases.

Please talk to your physician or pharmacist if you feel that the effect of UTESEL is too strong or too weak.

If you have used more UTESEL than you should

If you have used more UTESEL than you should, talk a physician or pharmacist.

If you forget to use UTESEL

Your doctor will decide when to administer the missed dose.

It is important that you follow your doctor's instructions for the new administration time of the following dose.

Do not take a double dose to make up for forgotten doses.

Effects which may occur when treatment with UTESEL is discontinued

No effects are expected.

4. What are the possible side effects?

Like all medicines, UTESEL may have side effects in people who are sensitive to the substances contained in its content.

If you notice any of the following, stop using UTESEL and inform your doctor IMMEDIATELY, or apply to the emergency service of the nearest hospital:

- Shortness of breath
- Pain in the chest
- Headache
- Palpitation
- Vomiting
- Pain, redness, swelling around the vein (thrombophlebitis)
- Confusion
- Contraction or seizure
- Bradycardia (slowed heart rate)

These are all very serious side effects.

If you have one of these, you have a serious allergy (hypersensitivity) to UTESEL. You may need an emergency medical intervention or hospitalization.

Headaches and seizures occur in one in a hundred people. Apart from headaches and seizures, all serious side effects are very rare (less than one in ten thousand people).

If you notice any of the following, inform your doctor IMMEDIATELY, or apply to the emergency service of the nearest hospital:

- Hypertension
- Hypotension
- Blood in urine (hematuria)
- Water poisoning
- Pale hand and foot
- Weakness in the feet
- Abnormal sweating
- Diarrhea
- Nasal congestion

All these are serious side effects.

If you have one of these, it means you have a serious allergy (hypersensitivity) to UTESEL. You may need emergency medical intervention or hospitalization.

Headaches and seizures occur in one in a hundred people. Apart from headache and seizures, all serious side effects are seen very rarely (less than one in ten thousand people).

All these are serious side effects. Immediate medical attention may be required. High blood pressure is seen in one in 100 people. Serious side effects other than high blood pressure are very rare (less than one in ten thousand people).

If you notice any of the following, inform your doctor:

- Dizziness
- Ringing in the ears
- Cramp
- Nausea
- Itching on the skin
- Rash on the skin
- Tongue rust taste

These are mild side effects of UTESEL. These side effects are uncommon (one in 100 people to one in 1000 people).

Reporting of the side effects:

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store UTESEL

Keep UTESEL out of the sight and reach of children, and in its packaging.

Store at room temperature below 25 ° C. Protect from light.

In addition, UTESEL should not be kept together with vitamin K and Hepatitis B vaccines applied in newborns to prevent misuse.

Use in compliance with the expiry date.

Do not use UTESEL after the expiry date on the package / carton / bottle / use before the expiry date.

The first two digits of the expiration date represent the month, and the last four digits indicate the year.

Do not use UTESEL if you notice any damage in the product and/or its package.

Do not throw away expired or unused medicines! Give it to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Authorization Holder and Manufacturer:

Osel İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Caddesi No: 52
Beykoz – İstanbul/ TURKEY
Tel : (0216) 320 45 51(Pbx)
Fax : (0216) 320 45 56

This patient information leaflet was approved on 11/06/2014.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

UTESEL 0.2 mg/1 mL I.M./I.V. ampoule containing solution for injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each 1 mL ampoule;

Metilergobasin maleate…….0.2 mg

Excipients:

Sodium chloride……..9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ampoule

Clear, colorless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

UTESEL is used:

- Prevention and treatment of uterine bleeding due to uterine atony or subinvolution after abortion, cesarean operations and postpartum
- In the second stage of labor, following the rise of the anterior shoulder while under complete obstetric supervision
- In incomplete abortion, it accelerates the excretion of uterine contents, in leechia

4.2. Posology and method of administration

Only clear and particulate-free ampoules should be used.

Posology /administrationfrequency and duration

The normal adult dose is usually 1 mL UTESEL (0.2 mg methylergobasin). If necessary, up to a maximum of 5 doses can be repeated at 2 to 4 hours intervals.

Method of Administration:

Intramuscular administration:

In uterine atony, after the arrival of the anterior shoulder or placenta, during the puerperium, and in the case of multiple babies, immediately after the birth of the last baby: 1 mL

Per day in puerperium, leech retention, uterine subinvolution: 0.25-1 mL
In cesarean section operations, during the birth of the baby into the uterine wall: 0.5 mL

Intravenous Administration:

Parenteral preparations containing methylergobasin maleate can only be administered intramuscularly (I.M.) in routine use. UTESEL should not normally be administered intravenously. Because there is a possibility of causing sudden hypertension and cerebrovascular accident. For life-threatening situations only, it may be given slowly over 60 seconds by the I.V route, with careful monitoring of blood pressure.

CAUTION: Do not exceed the specified doses and duration of use.
In patients who do not respond to UTESEL due to hypocalcemia, intravenous administration of calcium salts (provided that they have not taken digitalis before) may repeat the oxytocic action. If signs of ergotism occur, the administration of UTESEL should be discontinued immediately.

Additional information on special populations:

Renal / Hepatic impairment:

It should not be used in renal and hepatic diseases.

Pediatric population:

Its efficacy and safety in pediatric patients has not been studied.

Geriatric population:

Clinical studies with methylergobasin maleate do not include a sufficient number of patients aged 65 years and older to determine if a different response from younger ones is obtained. Other reported clinical experience did not reveal the difference in response in older and younger patients. Dose adjustment of elderly patients should be made with caution, and taking into account that reduced hepatic, renal or cardiac function and concomitant disease or other drug therapies are more common in this patient group, treatment should generally be initiated at the lowest dose within the dosing range.

4.3. Contraindications

- Hypertension
- Toxemia
- Pregnancy (See 4.6)
- In cases of hypersensitivity
- Concomitant use with potent cytochrome P450 (CYP) 3A4 inhibitor drugs is contraindicated.

4.4. Special warnings and precautions for use

UTESEL should not be routinely administered intravenously due to the possibility of causing sudden hypertension and cerebrovascular events. If intravenous administration is considered essential to save life, UTESEL (methylergobasin maleate) should be given slowly over 60 seconds and careful blood pressure monitoring must be done. Intra-arterial or periarterial injection should be avoided.

Coronary Artery Disease

People at risk of coronary artery disease or coronary artery disease (eg, smoking, obesity, diabetes, high cholesterol) are more likely to experience myocardial ischemia and infarction due to methylergobasin-induced vasospasm.

Abused

Symptoms reported in reports due to improper use of methylergobacin maleat in newborns include shortness of breath, convulsions, cyanosis and oliguria. Usually symptomatic treatment is performed. But in serious cases, respiratory and cardiovascular support is required. Since vitamin K and Hepatitis B vaccines used in newborns may be used inadvertently, UTESEL should be kept separately rather than together with the drugs administered in newborns in order to prevent such usage errors.

The patient should be followed carefully in sepsis, obliterative vascular disease, hepatic or renal failure. At the same time, attention should be paid in the second stage of birth. Manual removal of the remaining placenta is rarely required if sufficient time is allowed for spontaneous separation and appropriate techniques are applied.

UTESEL contains less than 23 mg sodium per 1 mL. No adverse effects are expected due to sodium.

4.5. Interaction with other medicinal products and other forms of interaction

CYP 3A4 inhibitors (e.g. macrolide antibiotics and protease inhibitors)

There have been rare reports of serious adverse events of vasospasm causing cerebral ischemia and / or ischemia of the extremities with the concomitant use of certain ergot alkaloid drugs (dihydroergotamine and ergotamine) with potent CYP 3A4 inhibitors. Potent CYP 3A4 inhibitors should not be used in combination with methylergobasin, although no interaction has been reported with methylergobasin alone. To more potent CYP 3A4 inhibitors, macrolide antibiotics (eg erythromycin, troleandomycin, clarithromycin), HIV protease or reverse transcriptase inhibitors (eg ritonavir, indinavir, nelfinavir, delavirdine) or azole antifungals (eg ketaconazole, itraconazole, varicillazole) can be given as an example. Less potent CYP 3A4 inhibitors should also be used with caution. Less potent inhibitors include saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole. This list is not exhaustive and the effect of other agents considered for use with methylergobasin maleate on the CYP 3A4 enzyme should be considered.

CYP 3A4 inducers

Nevirapine may reduce the pharmacological effects of methylergobacin maleat of potent CYP 3A4 inducers such as rifampicin.

Beta-Blockers

Methylergobacin maleate should be used with caution in combination with beta-blockers. Combined use with Beta-blockers may increase the vasoconstrictor effect of ergot alkaloids.

Anesthetics

Anesthetics such as halothane and methoxyflurane can reduce the oxytocic effect of methylergobacin maleat.

Glyceryl trinitrate and other antianginal drugs

Methylergobacin maleate is expected to reduce the effect of glyceryl trinitrate and other antianginal drugs due to vasoconstriction.

Pharmacokinetic interactions involving other cytochrome P450 isoenzymes are unknown.

UTESEL (methylergobacin maleate) other vasoconstrictors, ergot alkaloids, or attention should be paid when used at the same time as prostaglandins.

4.6 Pregnancy and lactation

General advice

Pregnancy category is C

Women with child-bearing potential / Contraception

Since UTESEL is indicated in postpartum and abortion, it is not used for this patient group.

Pregnancy

Due to its uterotonic effect, UTESEL is contraindicated during pregnancy (See 4.3), but it is used to restore the uterus after birth, reduce hemorrhage and shorten the third stage of labor.

Animal studies are insufficient for effects on pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development. The potential risk for humans is unknown.

Lactation

UTESEL should not be used during breastfeeding.

It has been reported that UTESEL reduces breast milk secretion and passes into breast milk. There are isolated reports of poisoning in breastfed babies after breastfeeding women use the drug for a few days. One or more of the following symptoms have been observed (and disappeared upon discontinuation of the drug) increased blood pressure, bradycardia or tachycardia, vomiting, diarrhea, restlessness, clonic cramps. UTESEL is not recommended to be used during breastfeeding due to the possibility of side effects on the child and the decrease in milk secretion.

After the last dose, you should wait at least 12 hours before breastfeeding.

Fertility

The effect of methylergobacin maleate on mutagenesis and fertility has not been determined.

4.7 Effects on ability to drive and use machines

No adverse effects on driving and using machines use have been reported. But due to the feeling of dizziness and the possibility of causing seizures, it is not recommended to drive and use machines during UTESEL use.

4.8 Undesirable effects

Reported undesirable effects are listed in the following order of frequency.

Very common ≥1/10; Common ≥1/100 to <1/10; Uncommon ≥1000 and <1/100;

Rare≥1/10000 and < 1/1000; Very rare <1/10000; Unknown (It can not be estimated from the available data).

Adverse reactions from clinical trials and post-marketing studies:

Blood and lymphatic system disorders

Very rare: Thrombophlebitis

Immune system disorders

Very rare: Anaphylaxis has been reported rarely in isolation, although its association with the drug has not been proven.

Nervous system disorders

Common: Headache, seizure

Very rare: Dizziness, ringing in the ears, hallucinations.

Cardiac disorders

Common: Hypertension

Rare: Transient chest pain, hypotension

Very rare: Acute myocardial infarction, arterial spasm (coronary and peripheral), bradycardia, tachycardia, palpitation.

Vascular disorders

Very rare: Leg cramps

Respiratory, thoracic and mediastinal disorders

Very rare: Shortness of breath (dyspnoea), nasal congestion.

Gastrointestinal disorders

Rare: Vomiting, nausea

Very rare: Diarrhea, taste of rust in the tongue

Skin and subcutaneous tissue disorders

Very rare: Sweating, rash.

Renal and urinary tract diseases

Very rare: Haematuria, water intoxication.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

The main symptoms of acute overdose are: nausea, vomiting, abdominal pain, loss of sensitivity, tingling in the extremities, hypertension, hypotension following hypertension in severe cases, respiratory depression, hypothermia, convulsions and coma.

A lethal dose in humans has not been established, as reports of methylergobasin overdose are uncommon. The oral LD_{50} (in mg/kg) is 187 in mice, 93 in rats and 4.5 in rabbits. Significant overdose of 0.2 mg has been reported in neonates who have been accidentally injected with methylergobasin maleate. However, there has been a return (recovery) in all cases. In only one case, respiratory depression, hypothermia, hypertonicity with sudden body movements, and in one case, a single convulsion occurred.

In addition, many children between the ages of 1-3 accidentally swallowed up to 10 tablets (2 mg), no signs of the disease were observed. A patient who gave birth accidentally took 4 tablets at once, the reported symptoms are paresthesia and a feeling of coldness.

Treatment of overdose is symptomatic and includes the following general procedures.

1. Removal of the drug by emesis, gastric lavage, purgation and supportive diuresis.
2. Ensuring adequate pulmonary ventilation, especially in case of convulsion or coma.
3. Correcting hypotension with vasopressor drugs, if necessary.
4. Controlling convulsions with standard anticonvulsant agents
5. When necessary, controlling peripheral vasospasm by warming the extremities.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic grup: Oxytocics / Ergot alkaloids

ATC code: G02AB01

The active substance of methylergobasin maleate contained in UTESEL directly affects the uterine smooth muscle, increasing the tone, speed and magnitude of rhythmic contractions of the uterus. It does not show a blocking effect on alpha-adrenergic receptors. Its clinical effect

is a result of stimulating smooth muscles. It causes a rapid and tetanic uterotonic effect, shortening the third stage of labor and reducing blood loss. The contraction of the uterine walls with bleeding vessels in the placental area stops the bleeding. The sensitivity of the uterus to the oxytocic effect is greater towards the end of pregnancy.

5.2 Pharmacokinetic properties

Absorption

Onset of effect in uterine contraction within 5-10 minutes when taken orally, it occurs within 2 to 5 minutes when administered intramuscularly, and immediately when administered intravenously. Bioavailability after oral administration without accumulation in repeated doses is about 60%. After intramuscular administration during childbirth its bioavailability can be up to 78%. Studies in healthy fasting female volunteers have shown that oral absorption of the tablet containing 0.2 mg of methylergobasin maleate is fairly rapid, with a mean peak plasma concentration (C_{max}) of 3243 ± 1308 pg/mL at 1.12 ± 0.82 hours (t_{max}). The mean peak plasma concentration (C_{max}) of 0.2 mg at 0.41 ± 0.21 hours) (tmax) at i.m. administration is 5918 ± 1952 pg / mL. The bioavailability of the tablet is the same as for the orally administered im solution, and the oral absorption of the im solution is proportional to the dose at the administration of 0.1, 0.2 and 0.4 mg. When administered intramuscularly, the absorption of methylergobasin maleate solution is 25% higher than that of the tablet. During treatment with methylergobasin maleate tablets, gastrointestinal absorption (t_{max} of approximately 3 hours) has been observed in postpartum women.

Distribution:

Pharmacokinetic studies show that, following iv injection, methylergobasin maleate rapidly diffuses from plasma to peripheral tissues in 2.3 minutes or less.

Its half-life is between 30 minutes and 2 hours. Its duration of action is approximately 3 hours when taken orally, approximately 3 hours when administered intramuscularly, and 45 minutes when administered intravenously. Here, rhythmic contractions can last up to 3 hours. The virtual volume of distribution (Vd) is 39-73 L.

Biotransformation:

Ergot alkaloids are metabolized in the liver, the decrease in bioavailability after oral intake is probably due to the first pass effect in the liver.

Elimination:

Less than 5% of the substance is excreted through the kidneys. Ergot alkaloids are generally excreted by hepatic metabolism and faeces. Half-life reflects two-phase (biphasic) elimination (1-5 minutes at the beginning, 0.5-2 hours at the end).

5.3 Preclinical safety data

In experimental animals, long-term studies have not been conducted to determine the possible carcinogenic effect of the drug, and its effect on mutagenesis and fertility has not been determined.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Thiourea
Sodium chloride
Tartaric acid
Water for injection

6.2 Incompatibilities

Ergot alkaloids, other vasoconstrictors, drugs containing these substances in local anesthetics, vasopressors.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store away from light, at room temperature below 25 ° C and in its packaging.

6.5 Nature and contents of container

1 mL amber colored Type I glass
It is presented in a cardboard box containing 3 and 50 ampoules.

6.6 Special precautions for disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

Osel İlaç San. ve Tic. A.Ş.

Akbaba Mah. Maraş Cad. No:52

Beykoz – İstanbul / TURKEY

Tel: 0 (216) 320 45 51

Fax: 0 (216) 320 45 56

8. MARKETING AUTHORISATION NUMBER

214/68

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorisation date: 06.03.2008

Renewal date of authorization: -

10. DATE OF REVISION OF THE TEXT