普洛舒定®-益二型陰道錠
PROSTIN® E_2 Vaginal Tablets

衛署藥輸字第 018215號
本藥須由醫師處方使用

成分
每錠含3毫克dinoprostone

劑型
陰道錠

臨床特性

適應症
對經產婦或順產婦之引產有效

劑量和給藥方法
本藥須由醫師處方使用
塞入一錠(3毫克)至後穹窿，使用後六至八小時如仍無法進行生產，可使用第二顆。在二十四小時之內，最高總投予劑量爲6毫克，不建議連續使用超過兩天。

禁忌症
不應用於對普洛舒定的成分(包括主成分Dinoprostone或其他賦形劑)過敏者。
對於有下列情況之病人應禁用普洛舒定及其他催產藥物：
多胎妊娠。
多胎史(曾有六次或六次以上足月懷孕者)。
胎兒頭部尚未進入產位。
曾動過子宮手術者(即：剖腹產，子宮切開術)。
胎兒頭部及母體骨盆不相稱。
疑有或確實證明胎兒窘迫的情形。
在產科無論是母體或是胎兒所做的風險評估，仍較適合手術時。
懷孕時發生無法解釋的陰道排出液或不正常的子宮出血。
非顱頂產式。

特殊警語及使用注意事項
當病人之心血管功能異常，肝、腎功能損害，患有氣喘，青光眼或眼內壓升高者，或羊膜及絨毛膜破裂時，使用普若舒定-益二型陰道錠產品應注意。
使用普若舒定-益二型陰道錠期間，需要密切監控子宮活動及胎兒心跳速率。當病人子宮張力過高、過度收縮，或是胎兒心跳速率異常等情形發生時，爲了產婦及胎兒的安全必須馬上給予完善的處理。
在使用任何催產劑時，應該要考慮造成子宮破裂的風險。
35歲以上婦女，在懷孕期出現併發症者以及妊娠期超過40週以上之產婦都被指出有增加分娩後血管內凝血的危險。更可能增加引產時的危險(參考**副作用**之說明)。因此這些婦女應小心使用普若舒定-益二型陰道錠。所以產婦在剛分娩後應盡快偵測是否有進行中的纖維溶解。
醫師應注意使用dinoprostone凝膠於子宮頸，可能造成抗原組織無預期崩解及栓塞，使少數的孕婦發生過敏反應(Anaphylactoid Syndrome)(羊膜液栓塞Amniotic Fluid Embolism)。

藥物交互作用
因爲前列腺素可能會加強催產素的作用，所以不建議同時併用其他的催產製劑。若要併用催產素，一般建議在使用普若舒定-益二型子宮頸凝膠，陰道內凝膠，或陰道錠後至少間隔六小時再使用催產素。

懷孕及哺乳
懷孕
普洛舒定-益二型使用於預產期及接近預產期懷孕婦女。
在老鼠與兔子的動物實驗中，前列腺素E_2的生成增加會造成骨骼異常。
目前已有證據顯示普若舒定-益二型具有胚胎毒性，給予任一劑量都會造成子宮張力持續上升，而對胚胎或胎兒造成威脅。(參考**特殊警語及使用注意事項**之說明)
哺乳
乳汁中僅含有微量前列腺素，而且在生下早產兒婦女及足月生產之婦女所分泌乳汁中測得含量並沒有顯著差異。

對儀器操作以及駕駛的影響
目前並無證據顯示對儀器操作以及駕駛有影響。

副作用
外用
產婦可能出現的副作用
根據報告，曾經使用子宮頸凝膠，陰道凝膠或陰道錠之產婦後續可能出現的副作用有：
免疫系統方面：過敏反應。
胃腸道方面：腹瀉，噁心，嘔吐。
骨骼肌肉與結締組織：背部疼痛。
懷孕期，產後，以及在產期前後時期：子宮不正常收縮(包括增加頻率，張力，持續時間)，子宮破裂。
生殖系統及乳房：陰道溫熱感。
全身性及給藥部位：發熱。
根據報告，以下副作用只有使用陰道錠產婦可能發生：
血管方面：高血壓。
呼吸道，胸腔及縱膈：氣喘，支氣管痙攣。
懷孕，產後，以及在產期前後時期：胎盤剝落，肺羊水栓塞，子宮頸迅速擴張。
胎兒可能出現的副作用
根據報告，曾經使用子宮頸凝膠，陰道凝膠或陰道錠產婦其胎兒可能出現下列副作用：
懷孕期，產後，以及在產期前後時期：死胎。
研究顯示：胎兒窘迫/胎兒心跳速率改變。
根據報告，以下副作用只有曾使用陰道錠產婦的胎兒可能發生：
懷孕期，產後，以及在產期前後時期：新生兒死亡。
全身性使用

產婦可能出現的副作用

根據報告，曾使用口服錠，滅菌溶液(1毫克/1毫升)的產婦後續可能出現的副作用有：

免疫系統方面：過敏反應。

神經系統方面：短暫血管迷走神經症狀(臉部潮紅，顫抖，頭痛，暈眩)。

心臟方面：心跳停止。

血管方面：高血壓。

呼吸道，胸腔及縱膈：氣喘，支氣管痙攣。

胃腸道：腹瀉，噁心，嘔吐。

皮膚及皮下組織：皮疹。

骨骼肌肉與結締組織：背部疼痛。

懷孕期，產後，以及在產期前後時期：子宮不正常收縮(包括增加頻率，張力，持續時間)，胎盤剝落，肺部羊水栓塞，子宮頸迅速擴張，子宮破裂。

全身性及給藥部位：發熱。

根據報告，以下副作用只有曾使用滅菌溶液(1毫克/1毫升)產婦可能發生：

全身性及給藥部位：注射部位局部組織刺激/紅斑。

研究顯示：白血球數目上升。

胎兒可能出現的副作用

根據報告，曾使用口服錠，滅菌溶液(1毫克/1毫升)產婦其胎兒可能出現下列副作用：

懷孕期，產後，以及在產期前後時期：新生兒死亡，死胎。

研究顯示：胎兒窘迫/胎兒心跳速率改變，新生兒窘迫/Apgar得分低。

上市後監視

血液及淋巴系統異常：藉由藥物(如普若舒定-益二型或催產素)引產時，可能會增加分娩後引發血管內血液凝集的風險(參考**特殊警語及使用注意事項**)。發生頻率很小(每1000名產婦中少於1人)。

藥物過量

前列腺素E_2具有過度刺激肌肉的特性，所以藥物過量可能呈現子宮過度收縮以及張力過高的情況。發生上列情形應給予適當的處理，即改變產婦姿勢以及給予母體氧氣補給。給予前列腺素E_2促使子宮頸成熟，其後續造成的過度刺激反應，可以使用乙型交感神經刺激劑(β-adrenergic)藥物來改善。

藥理學特性

藥效特性

作用機轉

刺激子宮：

普若舒定-益二型會刺激子宮肌肉像產程中的子宮一樣收縮，但目前尚未知本劑機轉是否直接作用在子宮肌肉層。不過在多數案例中，陰道給予普若舒定-益二型可造成子宮肌肉強烈收縮並且使子宮內受精卵排出。

子宮頸成熟：

普若舒定-益二型會導致子宮頸局部柔軟、擴張，以及子宮頸管消失。

上述變化一般從懷孕到預產期之間會自然發生，子宮頸的成熟會降低子宮頸的阻力伴隨著子宮肌肉的活動會增加，所以子宮內容物可以順利排出。

其他

普若舒定-益二型也會刺激人類胃腸道平滑肌，所以使用普若舒定-益二型引導子宮頸成熟時，偶爾會發生嘔吐或腹瀉等反應。

在實驗室動物及人類身上都發現，大量投予普若舒定-益二型會降低血壓，推測可能是藉由血管平滑肌的作用造成；此外，普若舒定-益二型還會提高體溫，但是使用引導子宮頸成熟的劑量尚未不會發生上述情形。

藥物動力學特性

主成分特性

吸收

以陰道內方式給予Dinoprostone吸收相當快速。使用子宮頸凝膠，約30～45分鐘之後血漿中濃度可達高峰值。Dinoprostone有73%會與人類血漿白蛋白結合。

若給予陰道凝膠造成血漿中前列腺素代謝物的增加量發現會明顯大於給予陰道錠，推測陰道凝膠有較佳生體可用率。

塞入陰道錠約40分鐘後，前列腺素E_2的吸收可達高峰值。

吞入口服錠15分鐘之後便可測得前列腺素E_2，吞入第一錠後約45分鐘可達高峰值。一小時後再吞入第二次錠並不會有蓄積的效果。

分佈與代謝

Dinoprostone在母體中可以廣泛分佈。

若以靜脈注射方式給予藥物的分佈及代謝都相當快速，給藥15分鐘後只有3%未被代謝藥物留在血液中。目前在人類的血液及尿液中可以測得九種以上的前列腺素E_2代謝物。

前列腺素E_2可以快速代謝成13,14-dihydro-15-keto 前列腺素E_2，再轉變成13-14-dihydro,15-keto前列腺素A_2。普若舒定-益二型在人類體內可以完全代謝。大部分先在肺部代謝之後再由肝臟及腎臟作進一步代謝。

排除

此藥物及其代謝物主要由腎臟代謝，小部分由糞便排出。

臨床前安全性資料

致癌性/致突變性/生育能力的損害：

因爲普若舒定-益二型只能使用在有限的適應症上，而且通常給藥期間短暫。所以目前針對致癌性生物分析研究的動物實驗尚未進行。而在Micronucleus test或Ames assay中並沒有發現普若舒定-益二型致突變的證據。

儲存需特別注意事項

儲存於2~8°C冰箱內。

瓶子一經打開，錠劑需在一個月內用完。

有效期限

有效期限標示於包裝上。

包裝

普洛舒錠-益二型陰道錠 4錠鋁箔盒裝。

版　本：CDS 711, 20080310

製造廠：Sanico N.V.

廠　址：Veedijk 59, Industriezone 4, 2300 Turnhout, Belgium

國外許可證持有者：Pfizer Manufacturing Belgium N.V.

廠　址：Rijksweg 12, 2870, Puurs, Belgium

藥　商：輝瑞大藥廠股份有限公司

地　址：台北縣淡水鎮中正東路二段177號

PROSTIN® E_2

Vaginal Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vaginal tablets containing 3 mg dinoprostone

PHARMACEUTICAL FORM

Vaginal Tablets

CLINICAL PARTICULARS

Therapeutic Indications

All indications are for pregnant women at or near term.Induction of labor.

Posology and Method of Administration

The initial dose is 1 tablet (3 mg) of dinoprostone inserted high into the posterior fornix. A second tablet may be inserted after 6-8 hours if labor has not been established. The maximum is 6 mg. Continuous administration of the drug for more than 2 days is not recommended.

Contraindications

Dinoprostone should not be used in patients with a hypersensitivity to dinoprostone or any other component of the product.

Dinoprostone should not be used in patients in whom oxytocic drugs are generally contraindicated such as:

- multiple gestation
- grand multiparity (6 or more previous term pregnancies)
- engagement of the head has not taken place
- previous uterine surgery (e.g., cesarean section, hysterotomy)
- cephalopelvic disproportion
- fetal heart rate pattern suggests incipient fetal compromise
- obstetric conditions where either maternal or fetal benefit/risk ratio favors surgical intervention
- unexplained vaginal discharge and/or abnormal uterine bleeding during current pregnancy
- nonvertex presentation

Special warnings and precautions for use

Dinoprostone products should be used with caution in patients with impaired cardiovascular, hepatic or renal function, asthma, glaucoma or raised intraocular pressure, or ruptured chorioamniotic membranes.

Continuous electronic monitoring of uterine activity and fetal heart rate should be conducted during use of dinoprostone. Patients who develop uterine hypertonus or hypercontractility, or in whom unusual fetal heart rate patterns develop, should be managed in a manner that addresses the welfare of the fetus and mother.

As with any oxytocic agent, the risk of uterine rupture should be considered.

Women aged 35 years or older, those with complications during pregnancy and those with a gestational age over 40 weeks have been shown to have an increased risk of post-partum disseminated intravascular coagulation. In addition, these factors may further increase the risk associated with labor induction (see section **Undesirable Effects**). Therefore, in these women, use of dinoprostone should be undertaken with caution. Measures should be applied to detect as soon as possible an evolving fibrinolysis in the immediate post-partum phase.

The Clinician should be alert that the intracervical placement of dinoprostone gel may result in inadvertent disruption and subsequent embolization of antigenic tissue causing in rare circumstances the development of Anaphylactoid Syndrome of Pregnancy (Amniotic Fluid Embolism).

Interaction with other medical products and other forms of interaction

The response to oxytocin may be accentuated in the presence of exogenous prostaglandin therapy. Concurrent use with other oxytocic agents is not recommended. The sequential use of oxytocin following administration of dinoprostone cervical gel, intravaginal gel, or vaginal tablets is recommended, with a dosing interval of at least 6 hours.

Pregnancy and lactation

Pregnancy

Dinoprostone is for use in pregnant women at or near term.

Prostaglandin E_2 produced an increase in skeletal anomalies in rats and rabbits. Dinoprostone has been shown to be embryotoxic in rats and rabbits, and any dose that produces sustained increased uterine tone could put the embryo or fetus at risk (see section **Special Warnings and Special Precautions for Use**).

Lactation

Prostaglandins are excreted in breast milk at very low concentrations. No measurable differences were observed in the milk of mothers delivering prematurely and at term.

Effects on ability to drive and use machines

Not applicable

Undesirable effects

Topical Use

Maternal Adverse Events. The following maternal adverse events have been reported with use of the cervical gel, intravaginal gel, and vaginal tablets:

Immune system disorders: Hypersensitivity reactions

Gastrointestinal disorders: Diarrhea, nausea, vomiting

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), uterine rupture

Reproductive system and breast disorders: Warm feeling in vagina

General disorders and administration site conditions: Fever

The following maternal adverse events have been reported only with use of the vaginal tablets:

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Pregnancy, puerperium and perinatal conditions: Abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation

Fetal Adverse Events. The following fetal adverse events have been reported with use of the cervical gel, intravaginal gel, and vaginal tablets.

Pregnancy, puerperium and perinatal conditions: Still births

Investigations: Fetal distress/altered fetal heart rate (FHR)

The following fetal adverse event has only been reported with vaginal tablets.

Pregnancy, puerperium and perinatal conditions: Neonatal death

Systemic Use

Maternal Adverse Events. The following maternal adverse events have been reported with use of the oral tablets and the sterile solution (1 mg/mL):

Immune system disorders: Hypersensitivity reactions

Nervous system disorders: Transient vasovagal symptoms (flushing, shivering, headache, dizziness)

Cardiac disorders: Cardiac arrest

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Asthma, bronchospasm

Gastrointestinal disorders: Diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders: Rash

Musculoskeletal and connective tissue disorders: Back pain

Pregnancy, puerperium and perinatal conditions: Uterine contractile abnormalities (increase frequency, tone, or duration), abruptio placenta, pulmonary amniotic fluid embolism, rapid cervical dilatation, uterine rupture

General disorders and administration site conditions: Fever

The following maternal adverse events have been reported only with use of the sterile solution (1 mg/mL):

General disorders and administration site conditions: Local tissue irritation / erythema (injection site)
Investigations: Elevated White Blood Cells (WBCs)

Fetal Adverse Events. The following fetal adverse events have been reported with use of the oral tablets and the sterile solution:

Pregnancy, puerperium and perinatal conditions: Neonatal death, still birth

Investigations: Fetal distress / altered FHR, neonatal distress / low Apgar score

Post-marketing surveillance:

Blood and lymphatic system disorders: An increased risk of post-partum disseminated intravascular coagulation has been described in patients whose labor was induced by pharmacological means, either with dinoprostone or oxytocin (see section **Special Warnings and Special Precautions for Use**). The frequency of this adverse event, however, appears to be rare (<1 per 1,000 labors).

Overdose

Overdosage may be expressed by uterine hypercontractility and uterine hypertonus. Because of the transient nature of PGE_2-induced myometrial hyperstimulation, nonspecific, conservative management was found to be effective in the vast majority of the cases; i.e., maternal position change and administration of oxygen to the mother. B-adrenergic drugs may be used as a treatment of hyperstimulation following administration of PGE_2 for cervical ripening.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of Action/Effect

For uterine stimulation

Dinoprostone stimulates the myometrium of the gravid uterus to contract in a manner that is similar to the contractions seen in the term uterus during labor. Whether or not this action results from a direct effect of dinoprostone on the myometrium has not been determined. Nonetheless, the myometrial contractions induced by the vaginal administration of dinoprostone are sufficient to produce evacuation of the products of conception from the uterus in the majority of cases.

For cervical ripening

Dinoprostone has a local cervical effect in initiating softening, effacement, and dilation. These changes, referred to as cervical ripening, occur spontaneously as the normal pregnancy progresses toward term and allow evacuation of uterine contents by decreasing cervical resistance at the same time that myometrial activity increases.

Other actions

Dinoprostone is also capable of stimulating smooth muscle of the gastrointestinal tract in humans. This activity may be responsible for the vomiting and/or diarrhea that is occasionally seen when dinoprostone is used for preinduction cervical ripening.

In laboratory animals, and also in humans, large doses of dinoprostone can lower blood pressure, probably as a result of its effect on smooth muscle of the vascular system. Dinoprostone can also elevate body temperature; however, with the dose of dinoprostone used for cervical ripening, these effects have not been seen.

Pharmacokinetic Properties

General characteristics of active substance

Absorption

When administered vaginally, dinoprostone is rapidly absorbed. Peak plasma concentrations of the cervical gel formulation are achieved in 30-45 minutes. Dinoprostone is 73% bound to human plasma albumin.

The increase in prostaglandin metabolites in plasma was significantly greater with the vaginal gel than with the vaginal tablet suggesting that the gel may have greater bioavailability.

Following insertion of the vaginal tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) increases to reach a peak at about 40 minutes.

Following ingestion of the oral tablet, PGE_2 absorption (as measured by the presence of PGE_2 metabolites) was detectable at 15 minutes, with a peak level occurring at about 45 minutes after the first oral dose. There was little evidence of accumulative effects when a second dose was administered after one hour.

Distribution and Metabolism

Dinoprostone is widely distributed in the mother.

Intravenous administration results in very rapid distribution and metabolism, with only 3% of unchanged drug remaining in the blood after 15 minutes. At least nine prostaglandin E_2 metabolites have been identified in human blood and urine.

PGE_2 is rapidly metabolized to 13, 14-dihydro-15-keto PGE_2, which is converted to 13, 14-dihydro, 15-keto PGA_2. Dinoprostone is completely metabolized in humans. It is extensively metabolized in the lungs, and the resulting metabolites are further metabolized in the liver and kidney.

Elimination

The drug and its metabolites are excreted primarily by the kidneys, with a small amount excreted in the feces.

Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenic bioassay studies have not been conducted in animals with dinoprostone due to the limited indications for use and short duration of administration. No evidence of mutagenicity was observed in the Micronucleus Test or Ames Assay.

Storage conditions

Store in a refrigerator (2°~8°C)
Use tablets within one month of opening a bottle pack.

Expiry date

The expiry date is mentioned on the package after "EXP."(EXP.=expiry date)

Presentations

Prostin E_2™ Vaginal Tablets, containing 3 mg dinoprostone, are available in packs of 4 tablets.

Version: CDS 711, 20080310

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