諾瓦得士錠10公絲
Nolvadex Tablets 10mg

衛署藥輸字第022154號
◎本藥須由醫師處方使用

成份：
每錠含相當於 tamoxifen 10mg之 Tamoxifen Citrate Ph Eur。

適應症：
轉移性乳癌之治療
乳癌手術後之輔助療法

特性：
"諾瓦得士" (tamoxifen) 爲一以triphenylethylene爲基礎之非類固醇藥物，在不同的組織呈現複雜範圍的雌激素拮抗劑及雌激素協同劑的藥理作用。對於乳癌病人，在腫瘤，tamoxifem主要是作用爲抗雌激素劑，可避免雌激素與雌激素接受體結合。然而臨床上顯示此藥物對於對雌激素接受體呈陰性之腫瘤也有些助益，顯示tamoxifem可能有其他作用機轉。在臨床上，已認可tamoxifem可導致停經後婦女之血中總膽固醇及低密度脂蛋白濃度降低達10-20%。此外，tamoxifem也已被報導可維持停經後婦女之骨質密度。
"諾瓦得士"口服吸收快速，4~7小時內達到血中最高濃度。每日服用40mg，四週後，血中藥物濃度可達穩定狀態 (大約300ng/ml)。此藥物與血清白蛋白有高度結合率 (>99%)。"諾瓦得士"經由氫氧化、去甲基化及結合作用，產生幾個代謝物。這些代謝物具有與藥品本體相似之藥理作用，故有治療效果。此藥基本上經由糞便排出體外，藥品本身之半衰期大約爲7天左右，而其主要之血中代謝物N-desmethyltamoxifen的半衰期則爲14天。

用法用量：
成人 (含老年人)
每天20~40mg，可分爲一天兩次給藥，或一天一次給藥。

禁忌：
"諾瓦得士" 不應給予以前曾對本品或其任一成份過敏的病人。
孕婦不得服用"諾瓦得士"。雖然有少數報告指出婦女在服用"諾瓦得士"後，發生自發性流產、胎兒先天性之缺陷及胎兒死亡之現象，但無法確定與使用此藥有關聯。
在大白鼠、兔子及猴子所作之生殖毒性的研究，顯示並無致畸胎之作用。
對齧齒類動物，Tamoxifen對胎兒生殖道發育引起之變化與 oestradiol、ethynyloestradiol、clomiphene 及 diethylstilboestrol (DES) 所引起的變化類似。雖然此等變化之臨床相關性未明，但某些改變，尤其是陰道腺病 (adenosis)，與在胎兒時期曾暴露於DES之年輕女性所見的情形相似，這些年輕女性產生陰道或子宮頸之澄清細胞癌 (clear-cell carcinoma) 的風險爲千分之一。只有少數孕婦曾使用過tamoxifen，這些病例並未被報告造成胎兒時期曾暴露於tamoxifen之年輕女性隨後之陰道腺病或陰道及子宮頸澄清細胞癌。
應建議婦女在服用"諾瓦得士"時不要受孕，而且若仍有性行爲，應使用非荷爾蒙性的避孕方式。停經前之婦女在治療前須小心檢查，以排除孕婦。當婦女在服用"諾瓦得士"時或在停藥後兩個月內懷孕，應評估其對胎兒可能產生之風險。

注意事項：
部份停經前之婦女在以"諾瓦得士"治療乳癌時，月經會受到抑制。
當"諾瓦得士" 與 coumarin 類抗凝血劑併用時，抗凝血作用可能會明顯的增加。開始併用此二劑時，建議仔細監測病人。
"諾瓦得士" 與具細胞毒性製劑併用，會增加發生血栓栓塞的危險。
曾有報告指出，以"諾瓦得士" 治療時，子宮內膜癌之發生率會增加。其潛在機制未明，但可能與"諾瓦得士"的類雌性激素特性有關。任何正在服用或曾服用本品之病人，若有不正常之婦科症狀，特別是陰道出血情形應儘速檢查。
在一系列於體外和體內進行之突變性試驗，證實 Tamoxifen 不具基因突變性。在某些體外試驗及齧齒類動物的體內基因毒性試驗中，顯示 Tamoxifen 具基因毒性。在長期之研究曾報告，接受 Tamoxifen 的小白鼠有性腺腫瘤，而大鼠有肝腫瘤，但這些發現之臨床相關性尚未被確立。
一些臨床報告曾指出，乳癌病人在以 Tamoxifen 治療後，有一些其他的原發性腫瘤發生於子宮內膜及另一側乳房以外之部位，然其因果關係尚未確立，而且這些發現之臨床意義仍然未明。
授乳："諾瓦得士"是否會分泌於乳汁中尚未知，故不建議授乳婦女使用。至於應停止授乳或停用"諾瓦得士"，應視此藥對母親的重要性來決定。

副作用：
本品之副作用可分爲因其藥理作用所引起之副作用，如熱潮紅、陰道出血、陰道分泌物、外陰搔癢及腫瘤加劇 (tumor flare)；或屬於比較一般性之副作用，如：
胃腸不適、頭昏眼花、頭痛及偶而有體液滯留和禿髮現象。
若以上之副作用情況嚴重時，可能可以藉由降低劑量 (在建議劑量範圍內) 而不減少對病情之控制的方式來控制。
少數有癌症轉移至骨頭的病人，在以本品治療初期會出現高血鈣症。
曾有報告指出，服用本品的乳癌病人，血小板數目會降低，通常只有降至 80,000~90,000/cu mm，但是有時會更少。
皮膚發疹 (包括多形紅斑 (erythema multiforme)、Stevens-Johnson 症候群及大水疱性類天疱瘡 (bullous pemphigoid))，及罕見之過敏反應 (包括血管水腫) 曾被報導。
有一些接受"諾瓦得士"治療的病人曾敘述有視力障礙 (包括角膜變化和視網膜之病變) 的情況。投與"諾瓦得士"錠曾被報導與白內障之發病率增加有關。
子宮肌瘤及子宮內膜改變 (包括增殖及息肉) 曾被報導。
停經前婦女服用"諾瓦得士"偶而有卵巢囊腫大。
在使用"諾瓦得士" 時，曾發生白血球減少症，有時伴隨有貧血及/或血小板減少症。嗜中性白血球減少症在罕見的情況下被報導過，這種情況有時會相當嚴重。
在使用"諾瓦得士"治療時，有跡象顯示血栓性栓塞 (包括深度靜脈栓塞及肺栓塞) 之發生率增加。在使用"諾瓦得士" 治療時，有一些跡象顯示這些事件之發生率增加。
當"諾瓦得士" 與有細胞毒性之藥物併用時，會增加血栓性栓塞發生之風險。
"諾瓦得士"與肝臟酵素量的變化有關，在極罕見之病例與一些較嚴重的肝功能異常，包括脂肪肝、膽汁鬱滯及肝炎等有關聯。
在罕見的情況下，血清三酸甘油酯濃度上升 (在某些病例併有胰臟炎)，可能與"諾瓦得士"的使用有關。

過量之處理：
理論上，過量應會增加上述因其藥理所引起的副作用。動物實驗顯示極度過量時 (每天劑量之 100~200 倍) 可能會產生雌性激素作用。
沒有特殊的解毒劑，需依症狀來治療。

貯藏：
儲存於 30°C 以下、避光。

其他資訊：
對於開車或操作機器之影響：無證據顯示"諾瓦得士"會減弱這些能力。

包裝：
4~1,000 粒盒裝。

製造廠：

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'NOLVADEX' TABLETS

Trade Mark

PRESENTATION

'Nolvadex' is available as tablets containing Tamoxifen Citrate Ph Eur equivalent to 10 mg of tamoxifen.

INDICATIONS

'Nolvadex' is indicated for the treatment of metastatic breast cancer and the adjuvant treatment of post-operative breast cancer.

PROPERTIES

'Nolvadex' (tamoxifen) is a non-steroidal, triphenylethylene-based drug which displays a complex spectrum of oestrogen antagonist and oestrogen agonist-like pharmacological effects in different tissues. In breast cancer patients, at the tumour level, tamoxifen acts primarily as an antioestrogen, preventing oestrogen binding to the oestrogen receptor. However, clinical studies have shown some benefit in oestrogen receptor negative tumours which may indicate other mechanisms of action. In the clinical situation, it is recognised that tamoxifen leads to reductions in levels of blood total cholesterol and low density lipoproteins in postmenopausal women of the order of 10–20%. Additionally tamoxifen has been reported to lead to maintenance of bone mineral density in postmenopausal women.

After oral administration, tamoxifen is absorbed rapidly with maximum serum concentrations attained within 4–7 hours. Steady state concentrations (about 300 mg/ml) are achieved after four weeks treatment with 40 mg daily. The drug is highly protein bound to serum albumin (>99%). Metabolism is by hydroxylation, demethylation and conjugation, giving rise to several metabolites which have a similar pharmacological profile to the parent compound and thus contribute to the therapeutic effect. Excretion occurs primarily via the faeces and an elimination half-life of approximately seven days has been calculated for the drug itself, whereas that for N-desmethyltamoxifen, the principal circulating metabolite, is 14 days.

DOSAGE AND ADMINISTRATION

Adults (including elderly): The dosage range is 20 to 40 mg daily, given either in divided doses twice daily or as a single dose once daily.

CONTRA-INDICATIONS

'Nolvadex' should not be given to patients who have experienced hypersensitivity to the product or any of its ingredients.

'Nolvadex' must not be given during pregnancy. There have been a small number of reports of spontaneous abortions, birth defects and foetal deaths after women have taken 'Nolvadex', although no causal relationship has been established.

Reproductive toxicology studies in rats, rabbits and monkeys have shown no teratogenic potential.

In rodent models of foetal reproductive tract development, tamoxifen was associated with changes similar to those caused by oestradiol, ethynyloestradiol, clomiphene and diethylstilboestrol (DES). Although the clinical relevance of these changes is unknown, some of them, especially vaginal adenosis, are similar to those seen in young women who were exposed to DES *in utero* and who have a 1 in 1000 risk of developing clear-cell carcinoma of the vagina cervix. Only a small number of pregnant women have been exposed to tamoxifen. Such exposure has not been reported to cause subsequent vaginal adenosis or clear-cell carcinoma of the vagina or cervix in young women exposed *in utero* to tamoxifen.

Women should be advised not to become pregnant whilst taking 'Nolvadex' and should use barrier or other non-hormonal contraceptive methods if sexually active. Premenopausal patients must be carefully examined before treatment to exclude pregnancy. Women should be informed of the potential risks to the foetus, should they become pregnant whilst taking 'Nolvadex' or within two months of cessation of therapy.

PRECAUTIONS

Menstruation is suppressed in a proportion of premenopausal women receiving 'Nolvadex' for the treatment of breast cancer.

When 'Nolvadex' is used in combination with coumarin-type anticoagulants, a significant increase in anticoagulant effect may occur. Where such co-administration is initiated, careful monitoring of the patient is recommended.

When 'Nolvadex' is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

An increased incidence of endometrial cancer has been reported in association with 'Nolvadex' treatment. The underlying mechanism is unknown, but may be related to the oestrogen-like effect of 'Nolvadex'. Any patients receiving or having previously received 'Nolvadex', who report abnormal gynaecological symptoms, especially vaginal bleeding, should be promptly investigated.

Tamoxifen was not mutagenic in a range of *in vitro* and *in vivo* mutagenicity tests. Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxicity tests in rodents. Gonadal tumours in mice and liver tumours in rats receiving tamoxifen have been reported in long-term studies. The clinical relevance of these findings has not been established.

A number of second primary tumours, occurring at sites other than the endometrium and the opposite breast, have been reported in clinical trials, following the treatment of breast cancer patients with tamoxifen. No causal link has been established and the clinical significance of these observations remains unclear.

Lactation: It is not known if 'Nolvadex' is excreted in human milk and therefore the drug is not recommended during lactation. The decision either to discontinue nursing or discontinue 'Nolvadex' should take into account the importance of the drug to the mother.

SIDE EFFECTS

Side effects can be classified as either due to the pharmacological action of the drug, e.g. hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae and tumour flare or as more general side effects, e.g. gastrointestinal intolerance, light-headedness, headache and occasionally, fluid retention and alopecia.

When such side effects are severe, it may be possible to control them by a simple reduction of dosage (within the recommended dose range) without loss of control of the disease.

A small number of patients with bony metastases have developed hypercalcaemia on initiation of therapy.

Falls in platelet count, usually only to 80,000–90,000 per cu mm but occasionally lower, have been reported in patients taking 'Nolvadex' for breast cancer.

Skin rashes (including isolated reports of erythema multiforme, Stevens-Johnson syndrome and bullous pemphigoid) and rare hypersensitivity reactions, including angioedema have been reported.

A number of cases of visual disturbances, including infrequent reports of corneal changes, and retinopathy have been described in patients receiving 'Nolvadex' therapy. An increased incidence of cataracts has been reported in association with the administration of 'Nolvadex'.

Uterine fibroids and endometrial changes including hyperplasia and polyps have been reported.

Cystic ovarian swellings have occasionally been observed in premenopausal women receiving 'Nolvadex'.

Leucopenia has been observed following the administration of Nolvadex, sometimes in association with anaemia and/or thrombocytopenia. Neutropenia has been reported on rare occasions; this can sometimes be severe.

There is evidence of an increased incidence of thromboembolic events, including deep vein thrombosis and pulmonary embolism, during 'Nolvadex' therapy. There is some evidence of an increased incidence of these events during 'Nolvadex' therapy.

When 'Nolvadex' is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events occurring.

'Nolvadex' has been associated with changes in liver enzyme levels and on rare occasions with a spectrum of more severe liver abnormalities including fatty liver, cholestasis and hepatitis.

Rarely, elevation of serum triglyceride levels, in some cases with pancreatitis, may be associated with the use of 'Nolvadex'.

OVERDOSAGE

On theoretical grounds, overdosage would be expected to cause enhancement of the pharmacological side effects mentioned above. Observations in animals show that extreme overdosage (100–200 times recommended daily dose) may produce oestrogenic effects.

There is no specific antidote and treatment must be symptomatic.

PHARMACEUTICAL PRECAUTIONS

Store below 30°C. Protect from light.

FURTHER INFORMATION

Effect on ability to drive or operate machinery: There is no evidence that 'Nolvadex' results in impairment of these activities.

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