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NOLVADEX NOLVADEX-D
ASTRAZENECA

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

'Nolvadex'-D is available as tablets containing Tamoxifen Citrate Ph. Eur. equivalent to 20 mg of tamoxifen.

Therapeutic indication
'Nolvadex' is indicated for the treatment of breast cancer.

Posology and method of 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.

Children: Not applicable

Contra-indications
Pregnancy: '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 (see also "Pregnancy and Lactation").

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

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

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) 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.

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.

Interactions
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 (see also "Undesirable effects").

As 'Nolvadex' is metabolised by cytochrome P450 3A4, care is required when co-administering with drugs, such as rifampicin, known to induce this enzyme as tamoxifen levels may be reduced. The relevance of this to clinical practice is not known.

Pregnancy and lactation
Pregnancy
'Nolvadex' must not be administered 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 or 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.

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.

Effect on ability to drive and operate machines

There is no evidence that 'Nolvadex' results in impairment of these activities.

Undesirable 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. gastro-intestinal intolerance, headache, light-headedness 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.

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

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.

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, endometriosis and other endometrial changes including hyperplasia and polyps have been reported.

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

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been associated with 'Nolvadex' treatment.

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. Very rarely, cases of interstitial pneumonitis have been reported.

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'.

Overdose

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 have been reports in the literature that Nolvadex given at several times the standard dose may be associated with prolongation of QT interval of the ECG.

There is no specific antidote to overdosage and treatment must be symptomatic.

Pharmacological properties

Pharmacodynamic properties

'Nolvadex' (tamoxifen) is a non-steroidal, triphenylene-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.

Pharmacokinetic properties

After oral administration, 'Nolvadex' is absorbed rapidly with maximum serum concentrations attained within 4-7 hours. Steady state concentrations (about 300 ng/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.

Pre-clinical safety data relevant to the prescriber

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.

Pharmaceutical precautions

Special precautions for storage

Do not store above 30oC. Store in original container.

Shelf life

Please refer to expiry date on blister strip and carton.

Pack size

Please refer to outer carton for pack size.

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February 2004