



TAMOPSINE 20MG TABLETS

PL 19156/0006

UKPAR

TABLE OF CONTENTS

| | |
|------------------------------------|---------|
| Lay Summary | Page 2 |
| Scientific discussion | Page 3 |
| Steps taken for assessment | Page 14 |
| Summary of Product Characteristics | |
| Product Information Leaflet | |
| Labelling | |

TAMOPSINE 20MG TABLETS

PL 19156/0006

LAY SUMMARY

The MHRA granted Pharmaceutical Services Incorporated (PSI) N.V. Marketing Authorisation (licence) for the medicinal product Tamopsine 20mg Tablets (PL 19156/0006). This is a prescription-only medicine (POM).

Tamopsine 20mg Tablets contains the active ingredient tamoxifen, which is one of a group of medicines called anti-oestrogen's. This product is used to treat breast cancer. It can also be used to treat infertility caused by a failure to ovulate properly.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Tamopsine 20mg Tablets outweigh the risks, hence Marketing Authorisation has been granted.

TAMOPSINE 20MG TABLETS

PL 19156/0006

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

| | |
|--|---------|
| Introduction | Page 4 |
| Pharmaceutical assessment | Page 5 |
| Preclinical assessment | Page 8 |
| Clinical assessment (including statistical assessment) | Page 9 |
| Overall conclusions and risk benefit assessment | Page 13 |

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisation for the medicinal product Tamopsine 20mg Tablets to Pharmaceutical Services Incorporated (PSI) N.V. on 10th May 2007. This prescription-only medicine (POM) is used for the treatment of breast cancer and anovulatory infertility.

This application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product of Nolvadex 20mg Tablets (PL 17901/0034) by Astra Zeneca UK Limited, first authorised on July 3rd, 1975 and January 1st 1982 respectively so the 10-year period of data exclusivity has expired.

Tamopsine (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. It is also 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%.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Tamoxifen citrate

CAS: 54965-24-1

Chemical name: (Z)-2-[4-(1,2-diphenylbut-1-enyl) phenoxy]ethylamine citrate

Structure

$C_{26}H_{29}NO$, $C_6H_8O_7$

Molecular Weight: 563.6

Tamoxifen citrate is a white or almost white powder. It is slightly soluble in water and acetone but soluble in methanol.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active tamoxifen citrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely calcium hydrogen phosphate dihydrate, microcrystalline cellulose, sodium starch glycollate, povidone K25 (E1201), magnesium stearate (E572), and colloidal anhydrous silica (E551). All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

No materials of animal or human origin are contained in or used in the manufacture of this product. A certificate has been provided to confirm that the magnesium stearate used is from plant origin.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce a product containing Tamopsine 20mg Tablets that are tolerable and which could be considered as generic medicinal product to the originator product Nolvadex 20mg Tablets.

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and Impurity profiles

Dissolution and impurity profiles for the drug product were found to be similar to that of the reference product.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in to PVC/Aluminium blisters. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions “Store in the original package” and “Do not store above 25 degree C” have been set, which are satisfactory.

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated. Satisfactory bioequivalence is seen between the test and reference product.

SPC, PIL, Labels

The SPC, PIL and Labels are pharmaceutically acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion

The proposed product has been shown to be a generic product of the reference product and has met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution profiles have been demonstrated for the proposed and reference products. It is recommended that Marketing Authorisation should be granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is a national standard abridged application for a marketing authorisation for Tamopsine 20mg submitted by PSI N.V. The application is made under article 10.1 of Directive 2001/83/EC as amended claiming to be a generic medicinal product of brand leader, Nolvadex 20 mg (PL 17901/0034), licensed to Astra Zeneca Ltd and first authorised in the Netherlands on 18th July 1975.

2. INDICATIONS

Tamopsine is indicated for:

1. The treatment of breast cancer.
2. The treatment of anovulatory infertility.

3. POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration: ORAL.

1. Breast cancer

Adults:

The recommended daily dose of tamoxifen is normally 20 mg. No additional benefit, in terms of delayed recurrence or improved survival in patients, has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40 mg per day is not available, although these doses have been used in some patients with advanced disease.

Elderly patients:

Similar dosing regimens of Tamopsine 20 mg have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

2. Anovulatory infertility

Before commencing any course of treatment, whether initial or subsequent, the possibility of pregnancy must be excluded. In women who are menstruating regularly, but with anovular cycles, the initial course of treatment consists of 20 mg given daily on the second, third, fourth and fifth days of the menstrual cycle. If unsatisfactory basal temperature records or poor pre-ovulatory cervical mucus indicate that this initial course of treatment has been unsuccessful, further courses may be given during subsequent menstrual periods, increasing the dosage to 40 mg and then to 80 mg daily.

In women who are not menstruating regularly, the initial course may begin on any day. If no signs of ovulation are demonstrable, then a subsequent course of treatment may start 45 days later, with dosage increased as above. If a patient responds with menstruation, then the next course of treatment is commenced on the second day of the cycle.

5. TOXICOLOGY

No toxicology data has been submitted or is required for this application. A toxicological expert report has been submitted.

6. CLINICAL PHARMACOLOGY

Pharmacokinetics.

A bio-equivalence study has been submitted comparing the 20mg Tamopsine Tablets with the equivalent dose of Nolvadex.

Bio-equivalence Study

This is a study investigating the pharmacokinetics, distribution and the relative bio-availability of tamoxifen in healthy volunteers. The study was an open label, fixed dose study.

Study Groups I and II were given either 20mg of Nolvadex or 20mg of Tamoxifen.

Results

The study report includes information on the 20mg formulations only.

Tamoxifen 20mg

There were no statistical differences between the treatment groups. Thus the 2 groups can be considered identical based on demographic criteria for age, weight, height and body surface area.

The statistical calculations for the bio-availability of tamoxifen and N-desmethyltamoxifen from the reference Nolvadex 20 mg and the applicant tamoxifen are shown in Tables 1 and 2, below:

Table 1:

Mean Pharmacokinetic Parameters of Tamoxifen after a Single Oral Dose of 20mg Tamoxifen (Nolvadex[®] 20 or Tamoxifen 20 Heumann)

| PHARMACOKINETIC | | NOLVADEX [®] 20 | | | | |
|------------------------------------|-----------|--------------------------|-------------|-------------|-------------|-------------|
| Parameter | n | mean | SD | CV(%) | Min | Max |
| C_{MAX} (NG/ML) | 18 | 31.0 | 8.8 | 28.4 | 18.8 | 56.9 |
| T_{MAX}(H) | 18 | 5.28 | 0.83 | 15.7 | 3.00 | 6.00 |
| AUC_{0-L} (NG·H/ML) | 18 | 2070 | 540 | 26.1 | 1230 | 3310 |
| AUC_{0-∞} (NG·H/ML) | 18 | 2250 | 570 | 25.3 | 1320 | 3510 |
| T_{1/2} (H) | 18 | 126 | 27 | 21.4 | 63.3 | 180 |

| PHARMACOKINETIC | | TAMOXIFEN 20 HEUMANN | | | | |
|------------------------------------|-----------|----------------------|-------------|-------------|-------------|-------------|
| Parameter | n | mean | SD | CV(%) | Min | Max |
| C_{MAX} (NG/ML) | 18 | 30.7 | 6.3 | 20.5 | 20.6 | 43.7 |
| T_{MAX}(H) | 18 | 5.31 | 1.30 | 24.5 | 2.50 | 8.00 |
| AUC_{0-L} (NG·H/ML) | 18 | 2030 | 470 | 23.2 | 1040 | 3120 |
| AUC_{0-∞} (NG·H/ML) | 18 | 2240 | 560 | 25.0 | 1140 | 3830 |
| T_{1/2} (H) | 18 | 138 | 33 | 23.9 | 69.7 | 217 |

Table 2:

Statistical Results of Testing Treatment with Tamoxifen 20 Heumann against Treatment with Nolvadex[®] 20 Using Mean Square Error Term From 2 Treatment ANOVA

| RESULTS FOR TAMOXIFEN | | | | | | |
|------------------------------|------|--------|-------|------------|----------------|----------|
| PARAMETER | DIFF | STAT | POWER | 90% SYM CL | 90% | |
| SHORTEST CL | (%) | | | (%) | | |
| C _{MAX} (NG/ML) | 0.8 | N.S.D. | 0.916 | 8.40 | 89.4 | TO 09.1 |
| T _{MAX} (H) | 0.6 | N.S.D. | 0.979 | 6.90 | 92.4 | TO 108.8 |
| AUC _{0-L} (NG·H/ML) | 2.1 | N.S.D. | 0.919 | 9.70 | 88.1 | TO 107.7 |
| AUC _{0-∞} (NG·H/ML) | 0.8 | N.S.D. | 0.906 | 8.50 | 89.2 | TO 109.2 |
| t _{1/2} (h) | 9.8 | n.s.d. | 0.928 | 17.2 | 100.2 to 119.4 | |

| RESULTS FOR N-DESMETHYLTAMOXIFEN | | | | | | |
|----------------------------------|------|--------|-------|------------|---------------|----------|
| PARAMETER | DIFF | STAT | POWER | 90% SYM CL | 90% | |
| SHORTEST CL | (%) | | | (%) | | |
| C _{MAX} (NG/ML) | 12.7 | N.S.D. | 0.433 | 26.9 | 69.0 | TO 105.7 |
| T _{MAX} (H) | 19.5 | N.S.D. | 0.236 | 40.0 | 54.0 | TO 107.1 |
| AUC _{0-L} (NG·H/ML) | 7.7 | N.S.D. | 0.865 | 16.0 | 97.0 | TO 118.5 |
| AUC _{0-∞} (NG·H/ML) | 6.1 | N.S.D. | 0.719 | 16.1 | 93.2 | TO 119.1 |
| t _{1/2} (h) | 8.5 | n.s.d. | 0.480 | 21.8 | 91.3 to 125.7 | |

Diff: Observed difference between means as % of reference mean

Stat: P value statistic

n.s.d.: no significant difference

90% Sym Cl: 90% confidence interval based on 2 one-sided t-tests ($\alpha=0.05$) expressed as % of reference mean + 100%

90% Shortest Cl: 90% confidence interval based on 2 one-sided t-tests ($\alpha=0.05$) expressed as % of reference mean + 100%

Study Conclusions

Bio-equivalence of 20mg Tamoxifen

The results demonstrate that Nolvadex 20 mg and the applicant Tamopsine formulation is bio-equivalent for tamoxifen. Bio-equivalence for the metabolite N-desmethyltamoxifen is also suggested by the results of this study.

Assessor' Comment**Bio-equivalence of 20mg Tamoxifen**

This study demonstrates bio-equivalence of the applicant formulation, Tamopsine 20mg to the references licensed Nolvadex 20mg.

In addition, it is reasonable to conclude from the data that the metabolite N-desmethyltamoxifen is also bio-equivalent.

7. EFFICACY

No clinical efficacy data is required for this application.

8. SAFETY

No clinical safety data is required for this application.

9. EXPERT REPORTS

The clinical expert report has been written by an appropriately qualified medic and it is satisfactory.

10. SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory.

11. PATIENT INFORMATION LEAFLET

The proposed PIL is satisfactory.

12. LABELLING

These are satisfactory.

13. MARKETING AUTHORISATION FORM

This is satisfactory.

14. DISCUSSION

The data presented demonstrates the bio-equivalence of the applicant Tamopsine 20mg to the reference Nolvadex 20mg.

With reference to the CPMP Note for Guidance on the Investigation of Bio-availability and Bioequivalence (CPMP/EWP/QWP/1401/98), this study seems well designed, conducted, analysed, and reported.

15. CONCLUSIONS

The applicant has demonstrated satisfactory bioequivalence with the innovator product. The clinical assessor recommends that marketing authorisation should be granted

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Tamopsine 20mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for application of this type.

EFFICACY

No new data were submitted and none are required for application of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Tamopsine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

TAMOPSINE 20MG TABLETS**PL 19156/0006****STEPS TAKEN FOR ASSESSMENT**

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation applications on 9 th September 2002 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the applications valid on 4 th November 2002 |
| 3 | Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 7 th April 2004, 7 th November 2003, and 13 th May 2005 and on the quality dossier 10 th February 2003 |
| 4 | The applicant responded to the MHRA's requests, providing further information on clinical dossier on 10 th October 2003, 23 rd January 2004 and 20 th June 2005 on the quality dossier on 10 th October 2003, 5 th November 2003, 3 rd March 2004, and 24 th November 2004 |
| 5 | The application was determined on 10 th May 2007 |

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Tamopsine 20 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

20 mg Tamoxifen (as citrate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, round and biconvex with embossing "20" on one side.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

Tamopsine 20 mg is indicated for:

1. The treatment of breast cancer.
2. The treatment of anovulatory infertility.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration: ORAL.

1. Breast cancer

Adults:

The recommended daily dose of tamoxifen is normally 20 mg. No additional benefit, in terms of delayed recurrence or improved survival in patients, has been demonstrated with higher doses. Substantive evidence supporting the use of treatment with 30-40 mg per day is not available, although these doses have been used in some patients with advanced disease.

Elderly patients:

Similar dosing regimens of Tamopsine 20 mg have been used in elderly patients with breast cancer and in some of these patients it has been used as sole therapy.

2. Anovulatory infertility

Before commencing any course of treatment, whether initial or subsequent, the possibility of pregnancy must be excluded. In women who are menstruating regularly, but with anovular cycles, the initial course of treatment consists of 20 mg given daily on the second, third, fourth and fifth days of the menstrual cycle. If unsatisfactory basal temperature records or poor pre-ovulatory cervical mucus indicate that this initial course of treatment has been unsuccessful, further courses may be given during subsequent menstrual periods, increasing the dosage to 40 mg and then to 80 mg daily.

In women who are not menstruating regularly, the initial course may begin on any day. If no signs of ovulation are demonstrable, then a subsequent course of treatment may start 45 days later, with dosage increased as above. If a patient responds with menstruation, then the next course of treatment is commenced on the second day of the cycle.

4.3 CONTRAINDICATIONS

Tamopside must not be given during pregnancy. Pre-menopausal patients must be carefully examined before treatment for breast cancer or infertility to exclude the possibility of pregnancy (see also section 4.6).

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

Treatment of infertility:

Patients with a personal history or family history of confirmed idiopathic venous thromboembolic events or a known genetic defect.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Menstruation is suppressed in a proportion of pre-menopausal women receiving Tamopside for the treatment of breast cancer.

An increased incidence of endometrial changes including hyperplasia, polyps, cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours), has been reported in association with Tamopside treatment. The underlying mechanism is unknown but may be related to the oestrogen-like properties of Tamopside. Any patient receiving or having previously received Tamopside who report abnormal gynaecological symptoms, especially vaginal bleeding, or who presents with menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure 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.

Venous thromboembolism:

- A 2-3-fold increase in the risk for VTE has been demonstrated in healthy tamoxifen-treated women (see section 4.8).

- In patients with *breast cancer*, prescribers should obtain careful histories with respect to the patient's personal and family history of VTE. If suggestive of a prothrombotic risk, patients should be screened for thrombophilic factors. Patients who test positive should be counselled regarding their thrombotic risk. The decision to use tamoxifen in these patients should be based on the overall risk to the patient. In selected patients, the use of tamoxifen with prophylactic anticoagulation may be justified (cross-reference section 4.5).

- The risk of VTE is further increased by severe obesity, increasing age and all other risk factors for VTE. The risks and benefits should be carefully considered for *all* patients before treatment with tamoxifen. In patients with *breast cancer*, this risk is also increased by concomitant chemotherapy (see section 4.5). Long-term anticoagulant prophylaxis may be justified for some patients with *breast cancer* who have multiple risk factors for VTE.

- Surgery and immobility: For patients being treated for *infertility*, tamoxifen should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when the patient is fully mobile. For patients with *breast cancer*, tamoxifen treatment should only be stopped if the risk of tamoxifen-induced thrombosis clearly outweighs the risks associated with interrupting treatment. All patients should receive appropriate thrombosis prophylactic measures and should include graduated compression stockings for the period of hospitalisation, early ambulation, if possible, and anticoagulant treatment.

- If *any* patient presents with VTE, tamoxifen should be stopped immediately and appropriate anti-thrombosis measures initiated. In patients being treated for *infertility*, tamoxifen should not be re-started unless there is a compelling alternative explanation for their thrombotic event. In patients receiving tamoxifen for *breast cancer*, the decision to re-start tamoxifen should be made with respect to the overall risk for the patient. In selected patients with *breast cancer*, the continued use of tamoxifen with prophylactic anticoagulation may be justified.

- *All* patients should be advised to contact their doctors immediately if they become aware of any symptoms of VTE.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

When Tamopsine 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 Tamopsine is used in combination with cytotoxic agents, there is increased risk of thromboembolic events occurring (see also sections 4.4 and 4.8). Because of this increase in risk of VTE, thrombosis prophylaxis should be considered for these patients for the period of concomitant chemotherapy.

As Tamopsine 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 clinical relevance of this reduction is unknown.

4.6 PREGNANCY AND LACTATION

Pregnancy:

Tamopsine 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 Tamopsine, 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, ethinyloestradiol, 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 Tamopsine and should use barrier or other non-hormonal contraceptive methods if sexually active. Pre-menopausal 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 Tamopsine or within two months of cessation of therapy.

Lactation:

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 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 side effects are severe, it may be possible to control them by a simple reduction of dosage (to not less than 20 mg/day) without loss of control of the disease. If side effects do not respond to this measure, it may be necessary to stop the treatment.

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 to 80,000 to 90,000 per cu mm but occasionally lower, have been reported in patients taking tamoxifen for breast cancer.

A number of cases of visual disturbance including reports of corneal changes and retinopathy have been described in patients receiving Tamopsine. An increased incidence of cataracts has been reported in association with the administration of Tamopsine.

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

Cystic ovarian swellings have occasionally been observed in pre-menopausal women receiving Tamopsine.

Leucopenia has been observed following the administration of Tamopsine, 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 Tamopsine therapy (see sections 4.3, 4.4 and 4.5). When Tamopsine is used in combination with cytotoxic agents, there is an increased risk of thromboembolic events.

Very rarely, cases of interstitial pneumonitis have been reported.

Tamopsine 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 Tamopsine.

An increased incidence of endometrial cancer and uterine sarcoma (mostly malignant mixed Mullerian tumours) has been reported in association with Tamopsine treatment.

4.9 OVERDOSE

On theoretical grounds, an 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 to overdosage, and treatment must be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Tamopsine (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%. Tamoxifen does not adversely affect bone mineral density.

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, tamoxifen 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.

5.3 PRECLINICAL SAFETY DATA

Tamoxifen was not mutagenic in a range of in-vitro and in-vivo mutagenicity tests. Tamoxifen was genotoxic in some in-vitro 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.

Tamoxifen is a drug on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Calcium Hydrogen Phosphate Dihydrate

Microcrystalline Cellulose (E460)

Sodium Starch Glycolate (Type A)

Povidone K25 (E1201)

Magnesium Stearate (E572)

Colloidal Anhydrous Silica (E551)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

2 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C. Store in the original package.

6.5 NATURE AND CONTENTS OF CONTAINER

Aluminium blister pack containing 30 or 250 tablets.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not applicable.

- 7 MARKETING AUTHORISATION HOLDER**
PSI n.v.
Kraanlei 27
9000 Ghent
Belgium
- 8 MARKETING AUTHORISATION NUMBER(S)**
PL 19156/0006
- 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
10/05/2007
- 10 DATE OF REVISION OF THE TEXT**
10/05/2007

PATIENT INFORMATION LEAFLET

Tamopsine 20 mg tablets

**Please read this carefully before you start to take your medicine.
This leaflet only gives a summary of the information available on your medicine.
If you have any questions, or are not sure about anything, ask your doctor or pharmacist.**

What you should know about your medicine?

The name of your medicine is 'Tamopsine'.

The active ingredient is tamoxifen. Your medicine also contains the following inactive ingredients: calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate and colloidal anhydrous silica.

'Tamopsine' is available as tablets that each contain 20 mg of tamoxifen.

'Tamopsine 20 mg tablets' are produced in packs of 30 and 250 tablets. Not all pack sizes may be available.

Tamoxifen is one of a group of medicines called anti-oestrogen's.

The manufacturer is:

Heumann Pharma GmbH
Nürnberger Straße 12
90537 Feucht
Germany

The product licence holder is:

PSI n.v.
Kraanlei 27
9000 Ghent
Belgium

Why use Tamopsine?

Tamopsine is used to treat breast cancer. It can also be used to treat infertility caused by a failure to ovulate properly.

Before taking your medicine

- Are you pregnant?
- Are you breast feeding?
- Are you taking any anticoagulant tablets?
- Have you ever had an allergic reaction to Tamopsine, or to any of its ingredients?
- Do you or your family have a history of blood clots or a known inherited condition leading to an increased risk of clotting?

If the answer is "yes" to any of these questions, tell your doctor or pharmacist. Tamopsine should not be taken by women who are pregnant or breast feeding and it can also interact with certain types of anticoagulant medicine, and a drug called rifampicin (for tuberculosis).

You should not become pregnant when taking Tamopsine. Please see your doctor for advice on what contraceptive precautions you should take, as some may be affected by Tamopsine. You should see your doctor immediately if you think you may have become pregnant after starting to take Tamopsine.

Warnings/Precautions while taking tamoxifen tablets

If you are sexually active, you should choose a barrier method or non-hormonal contraception. Discuss this with your doctor. If you think you have become pregnant you should speak to your doctor immediately.

If you are being treated for infertility, Tamopsine should be stopped at least 6 weeks before surgery or long-term immobility (when possible) and re-started only when you are fully mobile.

Taking your medicine

This medicine is only to be taken by mouth.

Follow your doctor's instructions about when and how to take your medicine. Also read the label. Your pharmacist can also help if you are not sure.

The usual dosage to treat breast cancer is 20 mg daily. The daily dose can either be taken as a single dose every day or the dose can be divided in two and taken in the morning and evening.

The dosage for infertility depends on the menstrual cycle. In women who are having regular periods, treatment usually begins by taking 20 mg of Tamopsine daily on the second, third, fourth and fifth days of the menstrual cycle.

If this is not successful, your doctor may increase the dosage on these days to 40 mg or 80 mg daily. In women who are not having regular periods (bleeding outside your normal menstruation), the treatment can be started on any day.

These tablets are not recommended for children.

What to do if you forgot to take a dose?

If you forget to take a dose, take it as soon as you remember and then carry on as before.

Never take two doses together.

After taking your medicine

As with all medicines, undesirable effects can sometimes be experienced with Tamopsine. Occasionally, a few people can suffer from stomach or gut upsets, headaches, lightheadedness, menstrual disturbances, hot flushes, genital itching, vaginal discharge or bleeding, fluid retention, hypertriglyceridemia (increased levels of fats in your blood) sometimes with pancreatitis (pain or tenderness in your upper abdomen), skin rashes or itching or peeling skin, thinning of the hair, or inflammation of the lungs (which may present with the same symptoms as pneumonia, such as breathlessness and cough).

Other possible effects are changes in vision or difficulty seeing properly as a result of cataracts or changes to the cornea or retina, an increased risk of blood clots, a tendency to bruise more easily, ovarian cysts or certain liver problems such as jaundice.

Other possible effects are those on the endometrium (lining of the womb) which may also be seen as vaginal bleeding or fibroids (causes enlargement of the womb) which may also be seen as discomfort in the pelvis or as vaginal bleeding.

It is important that you tell your doctor immediately if you have any unusual vaginal bleeding, menstrual irregularities, vaginal discharge or discomfort in the pelvis such as pain or pressure when you are taking Tamopsine or anytime afterwards. This is because a number of changes to the lining of the womb (the endometrium) may occur, some of which may be serious and could include cancer.

At the beginning of treatment for breast cancer, the symptoms of the disease can sometimes get worse, for example an increase in pain or an increase in the size of the affected tissue. In addition, if you get excessive nausea, vomiting or thirst, tell your doctor because this may mean that there are changes in the amount of calcium in your blood and your doctor may want to check on this.

Do not be alarmed by this list of possible effects. You may not experience any of them.

If you get any other undesirable effects or if you think your medicine is causing any problems, tell your doctor or pharmacist.

STOP TAKING Tamopsine and contact your doctor immediately in any of the following situations:

- If you develop symptoms of a blood clot such as calf or leg swelling, chest pain, shortness of breath or sudden weakness.
- If you develop difficulty in breathing with or without swelling of the face, lips, tongue and/or throat.
- If you develop swelling of the face, lips, tongue and/or throat which may cause difficulty swallowing.
- If you develop swelling of the hands, feet or ankles.
- If you develop urticaria ('nettle rash' or 'hives').

What to do if you take too many Tamopsine tablets?

If you or someone else swallows several of these tablets all together, contact your doctor, pharmacist or hospital emergency department immediately. Take the box and any remaining tablets with you in order to help identify the tablets.

Storing your medicine

Check the expiry date on the carton and don't use the medicine after that date.

Keep your medicine in a safe place where children cannot see it or reach it. Your medicine could harm them.

Do not store your medicine above 25°C. Store Tamopsine in the original package.

If your doctor decides to stop treatment, return any left-over tablets to your pharmacist. Only keep them if the doctor tells you to.

Date of preparation: February 2007

Further information

This leaflet does not contain the complete information on Tamopsine. If you have any questions, or are not sure about anything, ask your doctor or pharmacist.

Remember: This medicine is only for you. Only a doctor can prescribe it for you. Never give it to someone else.

It may harm them even if their symptoms are the same as yours.

The information applies only to Tamopsine.

LABELLING

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Tamopside 20 mg tablets
20 mg tamoxifen (as citrate)
PSI n.v.

Lot number : Expiry date :

Tamopside 20 mg tablets
[20 mg tamoxifen]

Each tablet contains 20 mg of tamoxifen (as citrate)

30 tablets

Lot number :
Expiry date :

Take as directed by the physician
Keep out of reach and sight of children
Please, read the enclosed leaflet carefully

POM

Tamopside 20 mg tablets
[20 mg tamoxifen]

Marketing Authorisation holder:
PSI n.v.
Kraanlei 27
B-9000 Ghent
Belgium
PL 19156/0006

Affix dispensing label here

For oral administration only
Do not store above 25°C
Store in the original package

