Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Letrozole 2.5mg Film Coated Tablets

UK/H/1159/01/DC
UK licence no: PL 30139/0005

Applicant: Intas Pharmaceuticals Limited

LAY SUMMARY

The MHRA granted Intas Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Letrozole 2.5mg Film Coated Tablets on 21st October 2008. This is a prescription-only medicine used to prevent breast cancer recurrences as first treatment after breast surgery or following five years of treatment with tamoxifen. Letrozole 2.5mg Film Coated tablets are also used to prevent breast tumour spreading to other parts of the body in patients with advanced disease. It can also be used to treat localised breast cancer in post-menopausal women before breast surgery.

These tablets contain the active ingredient letrozole. Letrozole belongs to agroup of medicines knowne as nonsteriodal aromatase inhibitors. Letrozole blocks the production of oestrogens.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Letrozole 2.5mg Film-Coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Product Name	Letrozole 2.5mg Film Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Letrozole
Form	Tablets
Strength	2.5mg
MA Holder	Intas Pharmaceuticals Limited Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom.
Reference Member State (RMS)	UK
CMS	Czech Republic, Hungary, Poland, Romania and Slovak Republic.
Procedure Number	UK/H/1159/01/DC
Timetable	Day 210– 8th September 2008

Module 2
Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Letrozole 2.5mg Tablets is as follows:

1. NAME OF THE MEDICINAL PRODUCT

Letrozole 2.5mg film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2.5 mg letrozole.
Each tablet contains 61.500 mg of lactose monohydrate. For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Yellow, round, biconvex, film coated tablets plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Extended adjuvant treatment of hormone–dependent early breast cancer in post menopausal women who have received prior standard adjuvant tamoxifen therapy for five years.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in women with natural or artificially induced post menopausal status after relapse or disease progression, who have previously been treated with anti-estrogens.
- Pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

4.2 Posology and method of administration

Adult and elderly patients

The recommended dose of letrozole is 2.5 mg once daily. No dose adjustment is required for elderly patients.

In the adjuvant setting, it is recommended to treat for 5 years or until tumor relapse occurs. In the adjuvant setting, clinical experience is available for two years (median duration of treatment was 25 months).

In the extended adjuvant setting, clinical experience is available for 3 years (median duration of treatment).

Children

Not recommended for use in children.

Patients with hepatic and/or renal impairment

No dosage adjustment is required for patients with renal insufficiency with creatinine clearance greater than 30 ml/min.

Insufficient data are available in case of renal insufficiency with creatinine clearance lower than 30 ml/min or in patients with severe hepatic insufficiency (see section 4.4 and 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.

- Premenopausal endocrine status; pregnancy; lactation (see section 4.6 and 5.3).

4.4 Special warnings and precautions for use

In patient whose postmenopausal status seems unclear, LH, FSH and/or oestradiol levels must be assessed before initiating treatment in order to clearly establish menopausal status.

Renal Impairment
Letrozole has not been investigated in a sufficient number of patients with creatinine clearance lower than 10 ml/min. The potential risk/benefit to such patients should be carefully considered before administration of letrozole.

Hepatic Impairment
Letrozole has only been studied in a limited number of non-metastatic patients with varying degrees of hepatic function: mild to moderate, and severe hepatic insufficiency. In non-cancer male volunteers with severe hepatic impairment (liver cirrhosis and Child-Pugh score C), systemic exposure and terminal half-life were increased 2-3-fold compared to healthy volunteers. Thus, letrozole should be administered with caution and after careful consideration of the potential risk/benefit to such patients (see section 5.2)

Bone Effects
Letrozole is a potent oestrogen-lowering agent. In the adjuvant and extended adjuvant setting the median follow-up duration of 30 and 39 months respectively is insufficient to fully assess fracture risk associated with long term use of letrozole. During adjuvant treatment with letrozole, women with osteoporosis and/or fractures or at risk of osteoporosis should have their bone mineral density formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment. Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by letrozole are not available, treatment for osteoporosis should be initiated as appropriate and patients treated with letrozole should be carefully monitored. (see section 4.8)

Lactose: This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Clinical interaction studies with cimetidine and warfarin indicated that the coadministration of letrozole with these drugs does not result in clinically significant drug interactions, even though cimetidine is a known inhibitor of one of the cytochrome P450 isoenzymes capable of metabolising letrozole *in vitro* (see section 5.2).
There was no evidence of other clinically relevant interaction in patients receiving other commonly prescribed drugs (e.g. benzodiazepines; barbiturates; NSAIDs such as diclofenac sodium, ibuprofen; paracetamol; furosemide; omeprazole).

There is no clinical experience to date on the use of Letrozole in combination with other anti-cancer agents.

Letrozole inhibits *in vitro* the cytochrome P450-isoenzymes 2A6 and moderately 2C19, however, CYP2A6 and CYP3A4 does not play a major role in drug metabolism. Thus, caution should be used in the concomitant administration of drugs whose disposition is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

4.6 Pregnancy and lactation

Pregnancy
Letrozole is contraindicated during pregnancy (see section 4.3 and 5.3).

Lactation
Letrozole is contraindicated during lactation (see section 4.3)

Women of perimenopausal status or child –bearing potential
The physician needs to discuss the necessity of a pregnancy test before initiating letrozole and of adequate contraception with women who have the potential to become pregnant including women who are perimenopausal or who have recently become post menopausal, until their post menopausal status is fully established (see sections 4.4 and 5.3).

There are no adequate data from the use of letrozole in pregnant women.

4.7 Effects on ability to drive and use machines

Since fatigue and dizziness have been observed with the use of letrozole and somnolence has been reported uncommonly, caution is advised when driving or using machines.

4.8 Undesirable effects

Letrozole was generally well tolerated across all studies as first-line and second-line treatment for advanced breast cancer, as adjuvant treatment of early breast cancer as well as in the treatment of women who have received prior standard tamoxifen therapy. Approximately one third of the patients treated with letrozole in the metastatic and neoadjuvant settings, approximately 70-75% of the patients in the adjuvant setting (both letrozole and tamoxifen arms), and approximately 40% of the patients treated following standard adjuvant tamoxifen (both letrozole and placebo arms) experienced adverse reactions. Generally, the observed adverse reactions are mainly mild or moderate in nature, and most adverse reaction can be attributed with normal pharmacological consequences of oestrogen deprivation.

The most frequently reported adverse reactions in the clinical studies were hot flushes, athralgia, nausea and fatigue. Many adverse reactions can be attributed to the normal pharmacological consequences of estrogen deprivation (e.g. hot flushes, alopecia and vaginal bleeding).

In the extended adjuvant setting, the following adverse events irrespective of causality were reported significantly more often with letrozole than with placebo – hot flushes (50.7% vs.44.3%), arthralgia/arthritis (28.5% vs. 23.2%) and myalgia (10.2% vs.7.0%). The majority of these adverse events were observed during the first year of treatment. The incidence of self-reported osteoporosis and bone fracture was higher in patients who received letrozole than in patients who received placebo (7.5% vs.6.3% and 6.7% vs.5.9%, respectively).

In the adjuvant setting, irrespective of casuality, the following adverse events occurred any time after randomization in the letrozole and tamoxifen groups respectively: thromboembolic events (1.5% vs. 3.2%, P<0.001), angina pectoris (0.8% vs. 0.8%), myocardial infarction (0.7% vs. 0.4%) and cardiac failure (0.9% vs. 0.4%, P=0.006).

The following adverse drug reactions, listed in Table 1, were reported from clinical studies and from post marketing experience with ~~L~~ letrozole.

Table 1

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to ≤ 1/100); rare (≥ 1/10000 to ≤ 1/1000); very rare (≤ 1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	
Uncommon:	Urinary tract infection
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Tumour pain [5]
Blood and the lymphatic system disorders	
Uncommon:	Leucopenia
Metabolism and nutrition disorders	
Common:	Anorexia, appetite increase, raised serum cholesterol
Uncommon:	General oedema
Psychiatric disorders	
Common:	Depression
Uncommon:	Anxiety [1]
Nervous system disorders	
Common:	Headache, dizziness
Uncommon:	Somnolence, insomnia, memory impairment, dysaesthesia [2], taste disturbance, cerebrovascular accident
Eye disorders	
Uncommon:	Cataract, eye irritation, blurred vision
Cardiac disorders	
Uncommon:	Palpitations, tachycardia
Vascular disorders	
Uncommon:	Thrombophlebitis [3] , hypertension, ischemic cardiac events [6]
Rare:	Pulmonary embolism, arterial thrombosis, cerebrovascular infarction
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough
Gastrointestinal disorders	
Common:	Nausea, vomiting, dyspepsia, constipation, diarrhoea
Uncommon:	Abdominal pain, stomatitis, dry mouth
Hepatobiliary disorders	
Uncommon:	Increased hepatic enzymes
Skin and subcutaneous tissue disorders	
Very common:	Increased sweating
Common:	Alopecia, rash [4]
Uncommon:	Pruritus, dry skin, urticaria
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia
Common:	Myalgia, bone pain, osteoporosis, bone fractures

Uncommon:	Arthritis
Renal and urinary disorders	
Uncommon:	Increased urinary frequency
Reproductive system and breast disorders	
Uncommon:	Vaginal bleeding, vaginal discharge, vaginal dryness, breast pain
General disorders and administration site conditions	
Very common:	Hot flushes, fatigue including asthenia
Common:	Malaise, peripheral oedema
Uncommon:	Pyrexia, mucosal dryness, thirst
Investigations	
Common:	Weight increase
Uncommon:	Weight loss

*Including:

(1) including nervousness, irritability
(2) including paraesthesia, hypoaesthesia
(3) including superficial and deep thrombophlebitis
(4) including erythematous, maculopapular, psoriaform and vesicular rash
(5) in metastatic/neoadjuvant setting only
(6) in the adjuvant setting, irrespective of causality, the following adverse events occurred in the letrozole and tamoxifen groups respectively: thromboembolic events (1.2% vs. 3.0%), angina pectoris (0.8% vs. 0.8%), myocardial infarction (0.5% vs. 0.4%), cardiac failure (0.8% vs. 0.3%).

4.9 Overdose

Isolated cases of overdose with letrozole have been reported.

No specific treatment for overdose is known; treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzyme inhibitors.

ATC Code: L02B G04

Pharmacodynamic effects

The elimination of oestrogen-mediated stimulatory effects is a prerequisite for tumour response in cases where the growth of tumour tissue depends on the presence of oestrogens and endocrine therapy is used. In postmenopausal women, oestrogens are mainly derived from the action of the aromatase enzyme, which converts adrenal androgens - primarily androstenedione and testosterone - to oestrone (E1) and oestradiol (E2). The suppression of oestrogen biosynthesis in peripheral tissues and the cancer tissue itself can therefore be achieved by specifically inhibiting the aromatase enzyme.

Letrozole is a non-steroidal aromatase inhibitor. It inhibits the aromatase enzyme by competitively binding to the haem of the cytochrome P450 subunit of the enzyme, resulting in a reduction of oestrogen biosynthesis in all tissues where present.

In healthy postmenopausal women, single doses of 0.1, 0.5, and 2.5 mg letrozole suppress serum oestrone and oestradiol by 75-78% and 78% from baseline respectively. Maximum suppression is achieved in 48-78h.

In postmenopausal patients with advanced breast cancer, daily doses of 0.1 to 5 mg suppress plasma concentration of oestradiol, oestrone, and oestrone sulphate by 75 - 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of oestrone and oestrone sulphate are below the limit of detection in the assays, indicating that higher oestrogen suppression is achieved with these doses. Oestrogen suppression was maintained throughout treatment in all these patients.

Letrozole is highly specific in inhibiting aromatase activity. Impairment of adrenal steroidogenesis has not been observed. No clinically relevant changes were found in the plasma concentrations of cortisol, aldosterone, 11-deoxycortisol, 17-hydroxy-progesterone, and ACTH or in plasma renin activity among postmenopausal patients treated with a daily dose of letrozole 0.1 to 5 mg. The ACTH stimulation test performed after 6 and 12 weeks of treatment with daily doses of 0.1, 0.25, 0.5, 1, 2.5, and 5 mg did not indicate any attenuation of aldosterone or cortisol production. Thus, glucocorticoid and mineralocorticoid supplementation is not necessary.

No changes were noted in plasma concentrations of androgens (androstenedione and testosterone) among healthy postmenopausal women after 0.1, 0.5, and 2.5 mg single doses of letrozole or in plasma concentrations of androstenedione among postmenopausal patients treated with daily doses of 0.1 to 5 mg, indicating that the blockade of oestrogen biosynthesis does not lead to accumulation of androgenic precursors. Plasma levels of LH and FSH are not affected by letrozole in patients, nor is thyroid function as evaluated by TSH, T4 and T3 uptake test.

Adjuvant treatment
A multicentre, double-blind study randomised over 8000 postmenopausal women with resected receptor-positive early breast cancer, to one of the following option:

Option 1:
A. tamoxifen for 5 years
B. Letrozole for 5 years
C. tamoxifen for 2 years followed by ~~L~~ letrozole for 3 years
D. Letrozole for 2 years followed by tamoxifen for 3 years.

Option 2:
A. tamoxifen for 5 years
B. Letrozole for 5 years

Data in Table 2 reflect results based on data from the monotherapy arms in each randomization option and data from the two switching arms up to 30 days after the date of switch. The analysis of monotherapy vs sequencing of endocrine treatments will be conducted when the necessary number of events has been achieved.

Patients have been followed for a median of 26 months, 76% of the patients for more than 2 years, and 16% (1252 patients) for 5 years or longer.

The primary endpoint of the trial was disease-free survival (DFS) which was assessed as the time from randomization to the earliest event of loco-regional or distant recurrence (metastases) of the primary disease, development of invasive contralateral breast cancer, appearance of a second non-breast primary tumour or death from any cause. Letrozole reduced the risk of recurrence by 19% compared with tamoxifen (hazard ratio 0.81; *P*=0.003). The 5-year DFS rates were 84.0% for letrozole and 81.4% for tamoxifen. The improvement in DFS with letrozole is seen as early as 12 months and is maintained beyond 5 years. Letrozole also significantly reduced the risk of recurrence compared with tamoxifen whether prior adjuvant chemotherapy was given (hazard ratio 0.72; *P*=0.018) or not (hazard ratio 0.84; *P*=0.044)

For the secondary endopoint overall survival a total of 358 deaths were reported (166 on letrozole and 192 on tamoxifen). There was no significant difference between treatments in overall survival (hazard ratio 0.86; *P*=0.15). Distant disease-free survival (distant metastatses), a surrogate for overall survival, differed significantly overall (hazard ration 0.73; P=0.001) and in

pre-specified stratification subsets. letrozole significantly reduced the risk of systemic failure by 17% compared with tamoxifen (hazard ration 0.83; P=0.02)

However, although in favour of letrozole non significant difference was obtained in the contralateral breast cancer (hazard ratio 0.61; P=0.09). An exploratory analysis of DFS by nodal status showed that letrozole was significantly superior to tamoxifen in reducing the risk of recurrence in patients with node positive disease (HR 0.71; 95% CI 0.59, 0.85; P=0.0002) while no significant difference between treatments was apparent in patients with node negative disease (HR 0.98; 95% CI 0.77, 1.25; P=0.89).This reduced benefit in node negative patients was confirmed by an exploratory interaction analysis (p=0.03).

Patients receiving letrozole, compared to tamoxifen, had fewer second malignancies (1.9% vs 2.4%). Particularly the incidence of endometrial cancer was lower with letrozole compared to tamoxifen (0.2% vs 0.4%).

See Tables 2 and 3 that summarize the results. The analyses summarized in Table 4 omit the 2 sequential arms from randomization option 1, i.e. take account only of the monotherapy arms:

Table 2 Disease-free and overall survival (ITT population)

	Letrozole n=4003	**Tamoxifen n=4007**	**Hazard ratio (95% CI)**	***P* -value[1]**
Disease-free survival (primary) - event (protocol definition)	351	428	0.81 (0.70, 0.93)	0.0030
Systemic disease-free survival (secondary)	323	383	0.83 (0.72, 0.97)	0.0172
Distant disease-free survival (metastases) (secondary)	184	249	0.73 (0.60, 0.88)	0.0012
Contralateral breast cancer (invasive) (secondary)	19	31	0.61 (0.35, 1.08)	0.0910
Overall survival (secondary) number of deaths (total)	166	192	0.86 (0.70, 1.06)	0.1546
CI = Confidence interval [1] Logrank test, stratified by randomisation option and adjuvant chemotherapy				

Table 3 Disease-free and overall survival by nodal status and prior adjuvant chemotherapy (ITT population)

	Hazard Ratio, 95% CI for hazard ratio	**P-Value[1]**
Disease-free survival		
Nodal status - Positive - Negative	 0.71 (0.59, 0.85) 0.98 (0.77, 1.25)	 0.0002 0.8875
Prior adjuvant chemotherapy - Yes - No	 0.72 (0.55, 0.95) 0.84 (0.71, 1.00)	 0.0178 0.0435
Overall survival		
Nodal status - Positive - Negative	 0.81 (0.63, 1.05) 0.88 (0.59, 1.30)	 0.1127 0.5070

Prior adjuvant chemotherapy - Yes - No	 0.76 (0.51, 1.14) 0.90 (0.71, 1.15)	 0.1848 0.3951
Distant disease-free survival		
Nodal status - Positive - Negative	 0.67 (0.54, 0.84) 0.90 (0.60, 1.34)	 0.0005 0.5973
Prior adjuvant chemotherapy - Yes - No	 0.69 (0.50, 0.95) 0.75 (0.60, 0.95)	 0.0242 0.0184
CI = confidence interval [1] Cox model significance level		

Table 4 Primary Core Analysis: Efficacy endpoints according to randomization option monotherapy arms (ITT population)

Endpoint	Option	Statistic	Letrozole	Tamoxifen
DFS (Primary, protocol definition)	1	Events / n	100 / 1546	137 / 1548
		HR (95% CI), *P*	0.73 (0.56, 0.94), 0.0159	
	2	Events / n	177 / 917	202 / 911
		HR (95% CI), *P*	0.85 (0.69, 1.04), 0.1128	
	Overall	Events / n	277 / 2463	339 / 2459
		HR (95% CI), *P*	0.80 (0.68, 0.94), 0.0061	
DFS (excluding second malignancies)	1	Events / n	80 / 1546	110 / 1548
		HR (95% CI), *P*	0.73 (0.54, 0.97), 0.0285	
	2	Events / n	159 / 917	187 / 911
		HR (95% CI), *P*	0.82 (0.67, 1.02), 0.0753	
	Overall	Events / n	239 / 2463	297 / 2459
		HR (95% CI), *P*	0.79 (0.66, 0.93), 0.0063	
Distant DFS (Secondary)	1	Events / n	57 / 1546	72 / 1548
		HR (95% CI), *P*	0.79 (0.56, 1.12), 0.1913	
	2	Events / n	98 / 917	124 / 911
		HR (95% CI), *P*	0.77 (0.59, 1.00), 0.0532	
	Overall	Events / n	155 / 2463	196 / 2459
		HR (95% CI), *P*	0.78 (0.63, 0.96), 0.0195	
Overall survival (Secondary)	1	Events / n	41 / 1546	48 / 1548
		HR (95% CI), *P*	0.86 (0.56, 1.30), 0.4617	

	2	Events / n	98 / 917	116 / 911
		HR (95% CI), *P*	0.84 (0.64, 1.10), 0.1907	
	Overall	Events / n	139 / 2463	164 / 2459
		HR (95% CI), *P*	0.84 (0.67, 1.06), 0.1340	
P -value given is based on logrank test, stratified by adjuvant chemotherapy for each randomization option, and by randomization option and adjuvant chemotherapy for overall analysis				

The median duration of treatment (safety population) was 25 months, 73% of the patients were treated for more than 2 years, 22% of the patients for more than 4 years. The median duration of follow-up was 30 months for both letrozole and tamoxifen.

Adverse events suspected of being related to study drug were reported for 78% of the patients treated with letrozole compared with 73% of those treated with tamoxifen. The most common adverse events experienced with Letrozole were hot flushes, night sweats, arthralgia, weight increase, and nausea. Of these, only arthralgia occurred significantly more often with letrozole than with tamoxifen (20% vs 13% for tamoxifen). Letrozole treatment was associated with a higher risk of osteoporosis (2.2% vs 1.2% with tamoxifen). Overall, irrespective of causality, cardiovascular/cerebrovascular events were reported any time after randomization for similar proportions of patients in both treatment arms (10.8% for letrozole, 12.2% for tamoxifen). Amongst these, thromboembolic events were reported significantly less often with letrozole (1.5%) than with tamoxifen (3.2%) ($P<0.001$), while cardiac failure was reported significantly more often with letrozole (0.9%) than with tamoxifen (0.4%) ($P=0.006$).Amongst patients who had baseline values of total serum cholesterol within the normal range, increases in total serum cholesterol higher than 1.5 times the ULN were observed in 5.4% of the patients in the letrozole arm, compared with 1.1% in the tamoxifen arm.

Extended adjuvant treatment
In a multicentre, double-blind, randomised, placebo-controlled study, performed in over 5,100 postmenopausal patients with receptor-positive or unknown primary breast cancer, patients who had remained disease-free after completion of adjuvant treatment with tamoxifen (4.5 to 6 years) were randomly assigned either letrozole or placebo.

An updated analysis conducted at a median follow-up of around 39 months (70% of the patients being followed for at least 3 years) showed that letrozole reduced the risk of recurrence by 44% compared with placebo (hazard ratio 0.56; $P=\leq 0.00001$). The statistically significant benefit in DFS in favour of letrozole was observed regardless of nodal status – node negative: hazard ratio 0.49; $P=0.0004$; node positive: hazard ratio 0.58; $P=0.00007$.

For the secondary endpoint overall survival (OS) a total of 224 deaths were reported (109 letrozole, 100 placebo and 15 who switched from placebo to letrozole). Overall, there was no significant difference between treatments in OS (hazard ratio 0.80; $P=0.10$).

At this update, results (median duration of follow-up was 3 years) from the bone mineral density (BMD) substudy (222 patients enrolled) demonstrated that, at 3 years, compared to baseline, patients receiving letrozole were associated with greater decreases in BMD in the total hip (median decrease of 4% in hip BMD compared to a median decrease of 1.7% in the placebo group ($P=0.131$, adjusted for bisphosphonate use, $P=0.645$). Patients receiving letrozole were associated with a greater decrease in lumbar spine BMD although not significantly different.
Concomitant calcium and vitamin D supplementation was mandatory in the BMD substudy.

In the same update, results (median duration of follow-up was 47 months) from the Lipid substudy (310 patients enrolled) show no significant differences between the letrozole and placebo arms in total cholesterol or in any lipid fraction. In the updated analysis 7.7% of patients in the letrozole arm reported cardiovascular adverse events during treatment compared with 6.1% in the placebo arm. These events included myocardial infarction (letrozole 0.8%, placebo 0.6%); angina requiring surgical intervention (0.6% in each treatment arm), new or worsening

angina (letrozole 1.3% vs placebo 1.0%), thromboembolic events (letrozole 0.6%, placebo 0.3%) and cerebrovascular accident (letrozole 1.0% vs placebo 0.7%).

No significant differences were observed on global physical and mental summary scores, suggesting that overall, letrozole did not worsen quality of life relative to placebo. Treatment differences in favour of placebo were observed in patients` assessments with particularly the measures of physical functioning, bodily pain, vitality, sexual and vasomotor items. Although statistically significant these differences were not considered clinically relevant.

First-line treatment
One controlled double-blind trial was conducted comparing letrozole 2.5 mg to tamoxifen 20 mg daily as first-line therapy in postmenopausal women with advanced breast cancer. In this trial of 907 women, letrozole was superior to tamoxifen in time to progression (primary endpoint) and in overall objective response, time to treatment failure and clinical benefit.

The results are summarized in Table 5:

Table 5 Results at a median follow-up of 32 months

Variable	**Statistic**	**Letrozole n=453**	**Tamoxifen n=454**
Time to progression	Median	9.4 months	6.0 months
	(95% CI for median)	(8.9, 11.6 months)	(5.4, 6.3 months)
	Hazard ratio (HR)	0.72	
	(95% CI for HR)	(0.62, 0.83)	
	P	<0.0001	
Objective response rate (ORR)	CR+PR	145 (32%)	95 (21%)
	(95% CI for rate)	(28, 36%)	(17, 25%)
	Odds ratio	1.78	
	(95% CI for odds ratio)	(1.32, 2.40)	
	P	0.0002	
Overall clinical benefit rate	CR+PR+NC≥24 weeks	226 (50%)	173 (38%)
	Odds ratio	1.62	
	(95% CI for odds ratio)	(1.24, 2.11)	
	P	0.0004	
Time to treatment failure	Median	9.1 months	5.7 months
	(95% for median)	(8.6, 9.7 months)	(3.7, 6.1 months)
	Hazard ratio	0.73	
	(95% CI for HR)	(0.64, 0.84)	
	P	<0.0001	

Time to progression was significantly longer, and response rate was significantly higher for letrozole than for tamoxifen in patients with tumours of unknown receptor status as well as with positive receptor status. Similarly, time to progression was significantly longer, and response rate significantly higher for letrozole irrespective of whether adjuvant anti-oestrogen therapy had been given or not. Time to progression was significantly longer for letrozole irrespective of dominant site of disease. Median time to progression was almost twice as long for letrozole in patients with soft tissue disease only (median 12.1 months for letrozole, 6.4 months for tamoxifen), and in patients with visceral metastases (median 8.3 months for letrozole, 4.6 months for tamoxifen). Response rate was significantly higher for letrozole in patients with soft

tissue disease only (50% vs 34% for letrozole and tamoxifen respectively), and for patients with visceral metastases (28% letrozole vs 17% tamoxifen).
Study design allowed patients to *cross over* upon progression to the other therapy or discontinue from the study. Approximately 50% of patients ***crossed over*** to the opposite treatment arm and crossover was virtually completed by 36 months. The median time to ***crossover*** was 17 months (letrozole to tamoxifen) and 13 months (tamoxifen to Letrozole)

Letrozole treatment in the first-line therapy of advanced breast cancer resulted in a median overall survival of 34 months compared with 30 months for tamoxifen (logrank test P=0.53, not significant). Better survival was associated with letrozole up to at least 24 months. The survival rate at 24 months was 64% for the letrozole treatment group versus 58% for the tamoxifen treatment group. The absence of an advantage for letrozole on overall survival could be explained by the crossover design of the study.

The total duration of endocrine therapy (**"**time to chemotherapy**"**) was significantly longer for letrozole (median 16.3 months, 95% CI 15 to 18 months) than for tamoxifen (median 9.3 months, 95% CI 8 to 12 months) (logrank *P*=0.0047).

Pre-operative treatment:
A double blind trial was conducted in 337 postmenopausal breast cancer patients randomly allocated either letrozole 2.5mg for 4 months or tamoxifen for 4 months. At baseline all patients had tumours stage T2-T4c, N0-2, M0, ER and/or PgR positive and none of the patients would have qualified for breast-conserving surgery. There were 55% objective responses in the letrozole treated patients versus 36% for the tamoxifen treated patients ($p<0.001$) based on clinical assessment. This finding was consistently confirmed by ultrasound ($p=0.042$) and mammography ($p<0.001$) giving the most conservative assessment of response. This response was reflected in a statistically significantly higher number of patients in the letrozole group who became suitable for and underwent breast-conserving therapy (45% of patients in the ~~L~~ letrozole group versus 35% of patients in the tamoxifen group, $p=0.022$). During the 4 month pre-operative treatment period, 12% of patients treated with ~~L~~ letrozole and 17% of patients treated with tamoxifen had disease progression on clinical assessment.

Second-line treatment:
Two well-controlled clinical trials were conducted comparing two letrozole doses (0.5 mg and 2.5 mg) to megestrol acetate and to aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with anti-oestrogens.

Time to progression was not significantly different between letrozole 2.5 mg and megestrol acetate (*P*=0.07). Statistically significant differences were observed in favour of letrozole 2.5mgcompared to megestrol acetate in overall objective tumour response rate (24% vs 16%, *P*=0.04), and in time to treatment failure (*P*=0.04). Overall survival was not significantly different between the 2 arms (*P*=0.2).

In the second study, the response rate was not significantly different between letrozole 2.5 mg and aminoglutethimide (*P*=0.06). Letrozole 2.5 mg was statistically superior to aminoglutethimide for time to progression (*P*=0.008), time to treatment failure (*P*=0.003) and overall survival (*P*=0.002).

5.2 Pharmacokinetic properties

Absorption
Letrozole is rapidly and completely absorbed from the gastrointestinal tract (mean absolute bioavailability: 99.9%). Food slightly decreases the rate of absorption (median t_{max}: 1 hour fasted versus 2 hours fed; and mean C_{max}: 129 ± 20.3 nmol/l fasted versus 98.7 ± 18.6 nmol/l fed) but the extent of absorption (AUC) is not changed. The minor effect on the absorption rate is not considered to be of clinical relevance and therefore letrozole may be taken without regard to mealtimes.

Distribution
Plasma protein binding of letrozole is approximately 60%, mainly to albumin (55%). The concentration of letrozole in erythrocytes is about 80% of that in plasma. After administration of 2.5 mg ^{14}C-labelled letrozole, approximately 82% of the radioactivity in plasma was unchanged compound. Systemic exposure to metabolites is therefore low. Letrozole is rapidly and extensively distributed to tissues. Its apparent volume of distribution at steady state is about 1.87 ± 0.47 Ll /kg.

Metabolism and elimination
Metabolic clearance to a pharmacologically inactive carbinol metabolite is the major elimination pathway of letrozole (CL_m= 2.1 l /h) but is relatively slow when compared to hepatic blood flow (about 90 l /h). The cytochrome P450 isoenzymes 3A4 and 2A6 were found to be capable of converting letrozole to this metabolite

Formation of minor unidentified metabolites and direct renal and faecal excretion play only a minor role in the overall elimination of letrozole. Within 2 weeks after administration of 2.5 mg ^{14}C-labelled letrozole to healthy postmenopausal volunteers, 88.2 ± 7.6% of the radioactivity was recovered in urine and 3.8 ± 0.9% in faeces. At least 75% of the radioactivity recovered in urine up to 216 hours (84.7 ± 7.8% of the dose) was attributed to the glucuronide of the carbinol metabolite, about 9% to two unidentified metabolites, and 6% to unchanged letrozole.

The apparent terminal elimination half-life in plasma is about 2 days. After daily administration of 2.5 mg steady-state levels are reached within 2 to 6 weeks. Plasma concentrations at steady state are approximately 7 times higher than concentrations measured after a single dose of 2.5 mg, while they are 1.5 to 2 times higher than the steady-state values predicted from the concentrations measured after a single dose, indicating a slight non-linearity in the pharmacokinetics of letrozole upon daily administration of 2.5 mg. Since steady-state levels are maintained over time, it can be concluded that no continuous accumulation of letrozole occurs.

Age had no effect on the pharmacokinetics of letrozole.

Special populations

In a study involving 19 volunteers with varying degrees of renal function (24 hour creatinine clearance 9-116 m l/min) no effect on the pharmacokinetics of letrozole was found after a single dose of 2.5 mg. In a similar study involving subjects with varying degrees of hepatic function, the mean AUC values of the volunteers with moderate hepatic impairment (Child-Pugh score B) was 37 % higher than in normal subjects, but still within the range seen in subjects without impaired function. In a study comparing the pharmacokinetics of letrozole after a single oral dose in eight male subjects with liver cirrhosis and severe hepatic impairment (Child-Pugh score C) to those in healthy volunteers (N=8), AUC and $t_{1/2}$ increased by 95 and 187%, respectively. Thus letrozole should be administered with caution and after consideration of the potential risk/benefit to such patients.

5.3 Preclinical safety data

Letrozole showed a low degree of acute toxicity in rodents exposed up to 2000 mg/kg. In dogs letrozole caused signs of moderate toxicity at 100 mg/kg.

In repeated-dose toxicity studies in rats and dogs up to 12 months, the main findings can be attributed to the pharmacological action of the compound. Effects on the liver (increased weight, hepatocellular hypertrophy, fatty changes) were observed, mainly at high dose levels. Increased incidences of hepatic vacuolation (both sexes, high dose) and necrosis (intermediate and high dose females) were also noted in rats treated for 104 weeks in a carcinogenicity study. They may have been associated with the endocrine effects and hepatic enzyme-inducing properties of Letrozole. However, a direct drug effect cannot be ruled out.

In a 104-week mouse carcinogenicity study, dermal and systemic inflammation occurred, particularly at the highest dose of 60 mg/kg, leading to increased mortality at this dose level. Again it is not known whether these findings were an indirect consequence of the

pharmacological activity of Letrozole (i.e. linked to long-term oestrogen deprivation) or a direct drug effect.

Both *in vitro* and *in vivo* investigations on letrozole's mutagenic potential revealed no indications of any genotoxicity.

In the carcinogenicity studies no treatment-related tumours were noted in male animals. In female animals, treatment-related changes in genital tract tumours (a reduced incidence of benign and malignant mammary tumours in rats, an increased incidence of benign ovarian stromal tumours in mice) were secondary to the pharmacological effect of the compound.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Hypromellose Type 2910
Cellulose microcrystalline
Sodium starch glycolate Type A
Colloidal anhydrous silica
Magnesium stearate

Coating (Opadry 03B82927 yellow):
Hypromellose 6 cp E464
Titanium dioxide E171
Iron oxide yellow E172
Macrogol 400
Talc E553b

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Blister composed of clear 250µ polyvinyl chloride (PVC) film coated with 90 gsm polyvinylidene chloride (PVdC) and plain 25µ aluminum foil.
Pack size: 28 tablets

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Intas Pharmaceuticals Limited
Sage House
319, Pinner Road
North Harrow
Middlesex HA1 4 HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 30139/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/10/2008

10 DATE OF REVISION OF THE TEXT
21/10/2008

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Module 3
Patient Information Leaflet

INTAS

PACKAGE LEAFLET : INFORMATION FOR THE USER

LETROZOLE 2.5 mg FILM-COATED TABLETS

Letrozole

Read all of this leaflet carefully before you start taking this medicine
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Letrozole Tablets is and what it is used for

Letrozole belongs to a group of medicines known as nonsteroidal aromatase inhibitors. Letrozole blocks the production of oestrogens.
Letrozole tablet is used to prevent breast cancer recurrences as first treatment after breast surgery or following five years of treatment with tamoxifen.
Letrozole tablet is also used to prevent breast tumor spreading to other parts of the body in patients with advanced disease.
Letrozole tablet should be used only for oestrogen receptor-positive breast cancer and only in women after menopause i.e. cessation of periods.
It can also be used to treat localized breast cancer in post-menopausal women before breast surgery. Your doctor will arrange regular check-ups during this treatment period before surgery, as there is a risk that your disease could progress even whilst taking this medicine.

2. Before you take Letrozole Tablets

Do not take Letrozole Tablets if
- You are allergic to letrozole or any of the other ingredients of letrozole tablets.
- You still have periods, i.e. if you have not yet gone through the menopause.
- You are pregnant
- You are breast-feeding

Take special care with Letrozole Tablets
- If you have a severe kidney disease,
- If you have a severe liver disease,
- If you have a history of osteoporosis (thinning or wasting of bones) or bone fractures.

Taking other medicines:
- Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Children and adolescents (below 18 years)
Letrozole is not to be used in children or adolescents.

Older people (age 65 years and over)
Letrozole tablet can be used by people aged 65 years and over at the same dose as for other adults.

Taking Letrozole Tablets with food and drink:
- Taking food and drink has no influence on your treatment with Letrozole Tablets.

Pregnancy and breast-feeding:
- Letrozole tablets are not recommended during pregnancy and breast-feeding.

Ask your pharmacist or doctor for advice before taking any medicine.

Driving and using machines:
- Do not drive or operate machinery, if you feel dizzy, drowsy or weak. Make sure you are fit to drive or operate machinery.

Important information about some of the ingredients of Letrozole Tablets.
Each tablet contains 61.5 mg of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Letrozole Tablets

Always take letrozole tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

- The usual dose of letrozole tablets is one tablet once daily.

If you take more Letrozole Tablets than you should
If you accidentally take too many Letrozole tablets, than you have been told to take, or if someone else accidentally takes your medicine, contact your doctor or hospital for advice immediately. Take your medicine with you.
If you forget to take Letrozole Tablets
Do not take a double dose to make up for the forgotten dose, take it as soon as you remember. Then take your next dose as usual.

4. Possible side effects

Like all medicines, letrozole tablets can cause side effects, although not everybody gets them.

Most of the side effects are mild to moderate and will generally disappear after a few days to few weeks of treatment. Some of them such as hot flushes, hair loss or vaginal bleeding, may be due to the lack of estrogen in your body.

In studies of people treated with letrozole tablets, the following side-effects have been reported:

Very common side-effects (≥ 1/10)
- Hot flushes
- Arthralgia (pain in your joints)
- Fatigue
- Increased sweating

Common side-effects (≥ 1/100 to < 1/10)
- Appetite problems (loss of appetite or increased appetite)
- Raised cholesterol levels
- Depression (sad mood)
- Headache
- Dizziness
- Problems with the digestive system (feeling sick, vomiting, indigestion, constipation, diarrhoea)
- Loss or thinning of the hair

- Increased sweating
- Skin rash
- Pain in your muscles
- Bone problems (pain, bone thinning (osteoporosis), fractures)
- Fatigue (feeling tired)
- Swelling of the legs or feet due to fluid retention
- Weight gain
- Malaise (generally feeling unwell)

Uncommon side effects (≥ 1/1000 to ≤ 1/100)
- Urinary tract infections, increased frequency of urination
- Eye—disorders (eye irritation, blurred vision)
- Breast pain, tumor pain, abdominal pain.
- Palpitations, rapid heart rate (tachycardia) angina and heart attack (ischemic cardiovascular disease.
- General edema
- Stroke
- Decreased white blood cells which can lead to infections (leucopenia)
- Inflamed blood vessels
- Nervous disorders (anxiety, nervousness, irritability, memory problems, somnolence, insomnia)
- Hypertension (raised blood pressure)
- Impairment of sensation, especially that of touch.
- Breathlessness
- Liver problems
- Taste disorder, dry mouth, thirst
- Joint stiffness (arthritis)
- Skin disorders such as itching, (urticaria), dry skin.
- Fever
- Vaginal disorders (vaginal bleeding, vaginal discharge, vaginal dryness)
- Weight loss
- Dryness of mucous membrane
- Cough, dyspnoea

Rare side effects (≥ 1/10000 to ≤ 1/1000)
- Thrombosis (clotting in the blood vessels e.g. legs)
- Pulmonary embolism (a blood clot in the lungs)
- Cerebrovascular infarction

When you should seek immediate medical help
A few of the uncommon and rare side effects of letrozole tablets (occurring in 1 to 100 people in every 10,000) need immediate medical attention. These are angina, heart attack, thrombosis, pulmonary embolism and stroke. The symptoms which might suggest that you are developing this problem are shown below.
- Paralysis
- Coughing blood
- Pain in the chest, spreading to your arms or shoulders, neck, teeth or jaw, abdomen or back
- Unusual pains or swelling of your arms or legs
- Sudden shortness of breath
- Fainting
- Numbness or weakness in arm or leg or any part of the body
- Loss of coordination
- Vision changes
- Sudden severe headache
- Difficulty in speaking or breathing

If any of the side effects gets serious, or if you notice any side effects not listed in the leaflet, please tell your doctor or pharmacist.

5. How to store Letrozole Tablets

- Keep out of reach and sight of children.
- This medicinal product does not require any special storage conditions.
- Do not use the tablets after the expiry date stated on the carton and blister EXP. The expiry date refers to the last day of that month
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose off medicines no longer required. These measures will help to protect the environment.

6. Further information

What Letrozole Tablets contains:
Each film-coated tablet contains 2.5 mg letrozole.

The other ingredients are:
Core Tablet: lactose monohydrate, maize starch, hypromellose type 2910, sodium starch glycolate type A, cellulose microcrystalline, colloidal anhydrous silica, magnesium stearate.
Film coating: hypromellose 6 cp E464, titanium dioxide E171, iron oxide yellow E172, macrogol 400 & talc E553b.

What Letrozole Tablets looks like and content of the pack:
Letrozole Tablets 2.5 mg are yellow, round, biconvex, film coated tablets plain on both sides. Letrozole Tablets are packed in blisters of 28 tablets.

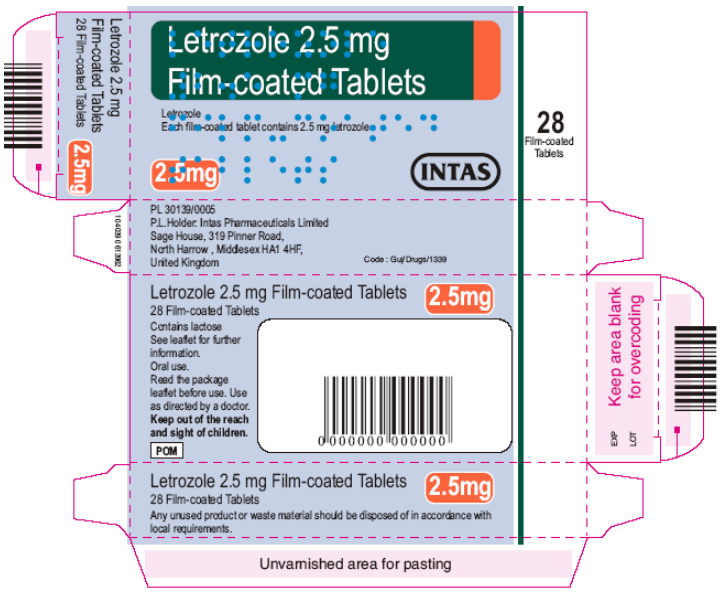
Marketing Authorisation Holder:
Intas Pharmaceuticals Limited, Sage House , 319 Pinner Road, North Harrow, Middlesex HA1 4HF, UK.

Manufacturer:
Accord Healthcare Limited, Sage House , 319 Pinner Road, North Harrow, Middlesex HA1 4HF, UK.

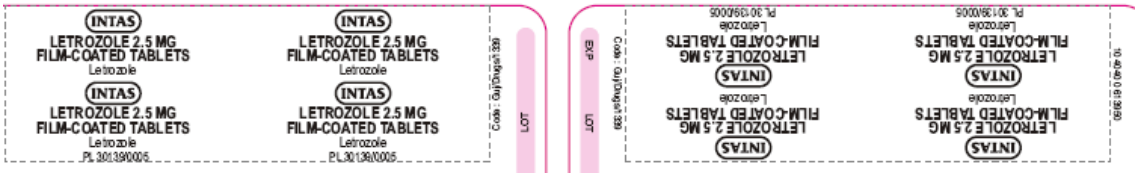
This leaflet was last approved October 2008

Module 4
Labelling

Letrozole 2.5mg Film-Coated Tablets
Carton



Blister Foil



Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for letrozole 2.5 mg tablets for the treatment of hormone receptor positive breast cancer, is approvable.

This abridged decentralised application concerns a generic version of Letrozole 2.5 mg Tablets submitted under Article 10.1. The originator product is Femara 2.5 mg tablets authorised to Novartis pharmaceuticals in January 1997 in the Netherlands and in September 1996 in the UK. The legal basis is satisfactory.

Letrozole is an aromatase inhibitor that is indicated for:

- Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.
- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer.
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.
- Pre-operative therapy in postmenopausal women with localized hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.

No new preclinical studies were conducted, which is acceptable given that the application is based on essential similarity to products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Letrozole 2.5mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Letrozole
Pharmacotherapeutic classification (ATC code)	Antineoplastic Agent (L02B G03)
Pharmaceutical form and strength(s)	2.5mg
Reference numbers for the Mutual Recognition Procedure	UK/H/1159/01/DC
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Hungary, Poland, Romania and Slovak Republic.
Marketing Authorisation Number(s)	PL 30139/0005
Name and address of the authorisation holder	Intas Pharmaceuticals Limited, Sage House, 319 Pinner Road, North Harrow, HA1 4HF, Middlesex, UK.

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

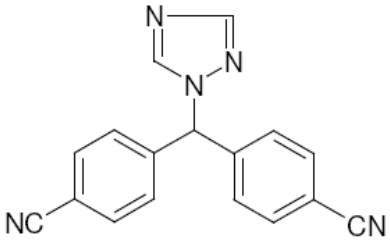
S. Active substance

INN name: Letrozole

Chemical names:
(i) 1-[bis(4-cyanophenyl)methyl]-1,2,4-triazole
(ii) 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-ylmethylene)bis-4,4'-(1H-1,2,4-triazol-1-ylmethylene) dibenzonitrile

CAS number: 112809-51-5

III.1.2 Structure



Letrozole

Molecular formula: $C_{17}H_{11}N_5$
Mr: 285.31 g/mol

III.1.3 General properties

Letrozole is a white to yellowish crystalline powder, which is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in methanol and slightly soluble in ethanol. No polymorphic forms have been reported in the literature. Letrozole has a melting point of 181-183 °C.

The drug substance is described in a monograph of the European Pharmacopoeia and the application is supported by a drug master file (DMF) provided by the drug substance manufacturer. The DMF has been assessed and is satisfactory.

The drug substance specification is in-line with the requirements of the Ph. Eur. Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug. Certificates of analysis have been provided for any working standards used.

P. Medicinal Product

Other Ingredients

Other ingredients consist of pharmaceutical excipients namely lactose monohydrate, maize starch, hypromellose Type 2910, cellulose microcrystalline, sodium starch glycolate Type A, colloidal anhydrous silica and magnesium stearate. All ingredients within the tablet core comply with relevant Ph Eur monographs.

The tablet coating (Opadry 03B82927 yellow) consists of: hypromellose 6cp E464, titanium dioxide E171, iron oxide yellow E172, macrogol 400 and talc E553b. All ingredients within the tablet coating comply with an in-house specification and is satisfactory.

With the exception of lactose monohydrate none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. A satisfactory declaration is provided from the supplier of magnesium stearate to confirm that the magnesium stearate is of vegetable origin. These statements are satisfactory and similar statements are provided from the suppliers of all of the excipients.

Pharmaceutical development

The purpose of formulation development was the development of a generic version that is “essentially similar” to the originator product, marketed by Novartis Pharma GmbH, Germany.

The objectives of the development programme was to develop a formula and a manufacturing process for Letrozole Film Coated Tablets, to produce tablets with the following

1) comparable dissolution profile to the brand
2) bioequivalent to the brand
3) meet all physical and chemical specifications for the dosage form in general and for this product.

Dissolution and impurity profiles

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

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Validation batch data from three pilot-scale batches have been provided and are satisfactory.

Finished Product Specification
The finished product specifications proposed are acceptable. 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
Letrozole tablets are packaged in blister packs composed of clear polyvinyl chloride (PVC) and film coated with polyvinylidene chloride (PVdC) and aluminium foil and is available in a pack size of 28 tablets. Specifications and certificates of analysis have been provided. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies have been performed on three pilot-scale batches with a commitment to provide the first three commercial scale batches when they become available. All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines. Based on the results of the stability studies, the applicant has proposed a shelf life of 3 years, with no specific storage conditions.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
The grant of a marketing authorisation is recommended.

III.2 PRE-CLINICAL ASPECTS

The pharmacological, pharmacokinetic and toxicological properties of letrozole are well known. As letrozole is a well known active substance, no further studies are required and the applicant has provided none. A satisfactory overview based on a literature review has been provided and is appropriate.

The non-clinical overview has been written by a suitably qualified person with experience in clinical pharmacology. The overview cites 29 references from the published literature which are dated from 1988 to 2005. The overview is adequate.

III.3 CLINICAL ASPECTS

Introduction
The clinical overview has been written by a medically qualified person. The clinical overview refers to 39 publications up to year 2006.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Clinical study reports

To support the application, the applicant has submitted as a report a single bioequivalence study which was conducted according to the principles of good clinical practice.

Pharmacokinetic studies (Project no. 045-06)

Methods

Study design 045-06

It was an open-label randomised, two-treatment, two period, two-sequence, single dose, crossover study, undertaken in adult, healthy male subjects under fasting conditions. Thirty subjects received study medication. Following a fast of at least 10-hours' single doses of study medication were administered with water according to a randomisation scheme. The treatment periods were separated by a wash-out period of 32-days'. During each treatment period serial blood sampling was undertaken prior to administration of study drug for up to 240-hours' after study drug administration.

Assessor's comment:
The study protocol and relevant materials were reviewed by an independent ethics committee. The study design is acceptable; the washout period is of an appropriate duration as is the sampling period.

Test and reference products

Letrozole 2.5 mg tablets manufactured by Intas Pharmaceuticals Ltd has been compared to Femara 2.5 mg tablets manufactured by Novartis Pharma GmbH for the UK market.

Population(s) studied

30 healthy male volunteers aged between 19 and 33 years' received at least one dose of study medication. 23 subjects successfully completed the study and their data were included in the statistical analysis. 2 subjects were withdrawn from the study fro medical reasons in Period II. 3 subjects discontinued the study for their own reasons and 2 subjects were discontinued because of pre-defined protocol deviations.

Analytical methods

Plasma concentrations of letrozole were determined using a validated LC-MS/MS method. The method is valid with respect to specificity, accuracy, precision, linearity, range, LOD/LOQ and robustness.

Pharmacokinetic Variables

The primary pharmacokinetic parameters for this study were peak plasma concentration (C_{max}) and area under the plasma concentration vs. time curve until last measured time point (AUC_{0-t}), area under the plasma concentration vs. time curve extrapolated to infinity ($AUC_{0-\infty}$). The secondary pharmacokinetic parameters were time to achieve peak plasma concentration (T_{max}), elimination rate constant (K_{el}) and plasma elimination half-life ($t_{½}$).

Statistical methods

The comparison of pharmacokinetic parameters was carried out using PROC MIXED of SAS release 9.1. ANOVA was carried out for un-transformed and in-transformed parameters. Two one-sided t test and confidence intervals were calculated to determine

the bioequivalence for the relevant pharmacokinetic parameters for the 23 subjects who completed both treatment groups

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	T_{max} h	$t_{1/2}$ h	K_{el} l/h
Test	1889.448 ±796.0305	2008.286 ±884.6797	38.092 ± 5.7102	2.000	44.059 ±15.9612	0.0179 ±0.00656
Reference	1850.993 ±753.8270	1962.981 ±856.7941	35.084 ± 7.4431	2.500	44.701 ±18.5194	0.0181 ±0.00701
***Ratio (90% CI)**	97.31 - 105.16	96.32 - 103.05	102.35 - 117.85			
CV (%)	7.6	6.5	14.0			

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration
$t_{1/2}$	half-life
Kel	elimination rate constant

**ln-transformed values*

Assessor's comment:
The 90% confidence intervals for AUC_{0-t} and C_{max} fall within the 80 to 125% confidence limits set out in the Note for Guidance on the Investigation of Bioavailability (CPMP/EWP/QWP/1401/98). There is also no significant difference between the plasma half-life and elimination rate constants of the test and reference products. According to the literature and the product information for the Innovator product food has a modest effect on the rate of absorption of letrozole, the extent of absorption is unchanged and it is not considered to be of clinical significance, therefore a bioequivalence study in fed subjects is not considered necessary.

Pharmacokinetic conclusion

Based on the submitted bioequivalence study Letrozole 2.5mg tablets are considered bioequivalent with Femara 2.5mg tablets.

Pharmacodynamic studies

None are required and none have been performed.

Additional data

Not applicable. Dissolution testing is discussed in the quality assessment report.

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

According to Volume 9 - Pharmacovigilance 1.4.2.5.2, less frequent submissions of PSURs than customary for new medicinal products can be appropriate. Femara was

granted a marketing authorisation in 1997 and also marketed since then in the Netherlands and the UK.

Letrozole has a well-recognised efficacy and an acceptable level of safety in the indications approved for Femara 2.5mg tablets, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

Benefit-Risk assessment
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

SUMMARY OF PRODUCT CHARACTERISTICS
The SPC is medically satisfactory.

PATIENT INFORMATION LEAFLET
The PIL is satisfactory.

LABELLING
Medically satisfactory.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Letrozole 2.5 mg 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 applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant's Letrozole 2.5mg Tablets and the reference product Femara 2.5mg Tablets (Novartis Pharma GmbH).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

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 letrozole is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome