European Medicines Agency

London, 06 November 2009
Doc Ref: EMA/311974/2010

CHMP ASSESSMENT REPORT FOR Arimidex 1 mg film-coated tablet

International Nonproprietary Name:
anastrozole

Procedure No: EMEA/H/A-29-PAD/1190

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier/Triggering of the procedure to the CHMP

AstraZeneca AB submitted on 29 April 2009 an application to the European Medicines Agency (EMEA) for Arimidex (anastrozole), and triggered a procedure under Article 29 of Regulation (EC) No 1901/2006, as amended. The CHMP was requested to give its opinion on the use of Arimidex 1mg film-coated tablets in the treatment of short stature in pubertal boys with growth hormone deficiency (GHD), in combination with exogenous growth hormone (GH).

Arimidex 1 mg film-coated tablets is registered in the following EU Member States/EEA countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and United Kingdom.

The eligibility of the centralised procedure for this application was agreed upon by the EMEA/CHMP on 23 April 2009.

The application was composed of administrative information, non-clinical and clinical data based on the MAHs' own studies and/or bibliographic literature.

Information relating to the PIP

Pursuant to Article 8 of Regulation (EC) No 1901/2006, as amended, the application included an EMEA Decision (P/20/2009):

- On the granting of a waiver for gynaecomastia and McCune-Albright syndrome.
- On the agreement of a paediatric investigation plan (PIP) for testotoxicosis and short stature due to growth hormone deficiency.

The PIP is completed. The PDCO issued a positive opinion on compliance with the PIP (EMEA-C-000283-PIP01-08).

2 SCIENTIFIC DISCUSSION

2.1 *Introduction*

Arimidex 1 mg film-coated tablets is currently indicated for the treatment of advanced breast cancer in postmenopausal women, as adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer, and adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

Arimidex has been approved in all Member States either by National approvals or through the Mutual Recognition Procedure. The current procedure under Article 29 of Regulation (EC) No 1901/2006, as amended, was initiated by AstraZeneca AB on behalf of the Marketing Authorisation Holders to obtain an extension of indication to include treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone. In order to support the application, the MAH submitted non-clinical and clinical documentation, including the results of clinical studies on the requested indication and on additional indications that provided specific information on paediatric use.

Following the initial assessment of the application and the objections raised by the CHMP, the MAH decided not to pursue the indication further and alternatively submitted a proposal for the update of the Product Information with the existing paediatric data as foreseen in Article 36 of Regulation (EC) No 1901/2006.

2.2 *Non-clinical aspects*

The applicant has submitted the results of one study dated 2002. A brief summary of this fertility study

in male rats following oral administration of the product is provided below.

As per the PDCO opinion for the anastrozole paediatric investigation plan, no additional non clinical studies have been conducted to support the use of anastrozole in pubertal boys as the existing non clinical data are considered sufficient to support the claimed indication.

Summary of the results of the fertility study in male rats – study number TGR3192

Groups of 24 weanling male rats were dosed orally with 0, 50 or 400 mg/L Zeneca ZD1033 (anastrozole) via their drinking water for 10 weeks and then were paired 1 to 1 with untreated females. At the end of the pairing period, half the males from each dose group were killed. Endpoints studied included organ weights and histopathology of the male reproductive tract plus sperm counts and motility (via computer assisted sperm analysis) and assessment of sperm morphology. The control and high dose group animals had a 9-week withdrawal period prior to pairing on a 1 to 1 basis with a second untreated female. Blood samples were collected on days 7 and 63 after 8 hours light and 8 hours of darkness to monitor exposure to the test compound. All females were killed on putative pregnancy day 12 or day 13 for uterine examination.

The results of the study indicate that anastrozole did not cause adverse effects on testis and epididymal weights, epididymal sperm function, sperm number or morphology. A reduction in anastrozole plasma concentration at the high dose level on day 63 of the study suggesting auto-induction of metabolising enzymes may have occurred during long term exposure to anastrozole. Mating indices were adversely affected at both 50 and 400 mg/L dose groups, while a reduction in fertility was evident only at the 400 mg/L dose group. The reductions on mating and fertility indices, together with reductions on body weight, and food and consumption were reversible following a 9 week treatment free recovery period.

The data revealed adverse treatment related effects on male reproduction the clinical significance of which have not been addressed by the applicant. There was a decrease in the number of pregnant females at the high dose. There was a decrease in the number of implantations and live fetuses at the high dose (an arithmetic mean of 13.7, 12.1 and 7.6 implantations and 13.4, 12.1 and 6.8 live fetuses at 0, 50 and 400 mg/L respectively) and an increase in the % post implantation loss (2.3, 0.5, and 40.8 at 0, 50 and 400mg/L respectively). This indicates a treatment related effect on the embryo. These effects occurred at systemic exposures which are relevant based on clinical exposures in pubertal boys (based on median Css, max in pubertal boys [41.4 ng/ml, range 17.2 to 75.6 ng/ml]. Although these adverse effects were not reported after a treatment free recovery period, the rats had been treated for only ten weeks whilst the proposed clinical treatment regimen is up to 3 years. There is no information of the effects of longer term treatment in the rat. There is no information on the toxicity to reproduction in the intended patient population for duration of treatment greater than one year. The age group of the intended patient population is up to a bone age of greater than 16 years of age and a growth rate of less than 2 cm/year. Therefore the possibility of these patients causing pregnancy cannot be excluded.

In conclusion, the existing preclinical information does not support the granting of a new paediatric indication. There is concern at the adverse treatment related effects on male fertility reported in the rat study at clinically relevant systemic exposure and their clinical relevance particularly in view of the proposed long term use of the product.

2.3 *Clinical aspects*

2.3.1 Introduction

The applicant has submitted efficacy data from a single pivotal study D5390L00074 (0074) to support the proposed paediatric indication ‘Treatment of short stature in pubertal boys with growth hormone deficiency (GHD), in combination with exogenous growth hormone (GH).’

Several additional studies were submitted in order to provide additional safety data, and to provide pharmacokinetic and pharmacodynamic data relevant to a paediatric population. Study 0047, on

testotoxicosis, was submitted as part of the PIP. Studies 0001, 0006 and 0046 concern paediatric populations for which a waiver has already been granted by the PDCO.

Study ID	No. of study centres	Design	Study posology	Number random-ised	Duration	Age range /gender	Diagnosis	Primary endpoint
D5390L00074 (0074)	7	Randomised, double-blind placebo-controlled trial	Anastrozole 1 mg + GH or placebo + GH	52	3 years	Boys 11-16	GH deficiency	Change in predicted adult height
D6873C00047 (0047)	10	Single arm open label study	Anastrozole + bicalutamide (dose titration)	14	1 year	Boys 2-9	Testotoxicosis	Change in growth rate
D5394C00001 (0001)	2	Single arm open label study	Anastrozole 1 mg	38	6 months	Boys 10-17	Pubertal gynaecomastia	PK/PD
D5394C00006 (0006)	24	Randomised, double-blind placebo-controlled trial	Anastrozole 1 mg	82	6 months	Boys 11-18	Pubertal gynaecomastia	Response rate
D5394C00046 (0046) (including PK sub-study 0000)	14	Single arm open label	Anastrozole 1 mg	28	1 year	Girls 2-10	McCune Albright Syndrome	Precocious puberty parameters

2.3.2 GCP

The Marketing Authorisation Holder has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.3 Pharmacokinetics

2.3.3.1 Pharmacokinetics in children

Study D5394C00001 (0001)

This was a single arm open label pharmacokinetic and pharmacodynamic study of anastrozole in pubertal boys with gynaecomastia of recent onset. Secondary objectives included assessment of efficacy and safety. Efficacy has not been demonstrated in this patient population.

Study participants were boys aged 11-18 with pubertal gynaecomastia of less than 12 months duration. Treatment was with anastrozole 1 mg tablet daily for 6 months. The pharmacokinetic assessment was carried out at least 14 days after the first dose, following at least 7 days of consecutive dosing. Subjects fasted for 6-8 hours before the assessment, and for 2 hours post dose. Blood samples were taken before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post dose.

Summary statistics for PK parameter estimates for anastrozole following multiple oral administration of anastrozole 1 mg (PK population)

Parameter	Statistic					
	N	Geometric mean	CV%	Median	Minimum	Maximum
$C_{ss,max}$(ng/ml)	36	39.3	34.3	41.4	17.2	75.6
t_{max}(hr)	36	-	-	1.00	0.50	3.00
$C_{ss,\ min}$(ng/ml)	36	21.5	44.1	22.1	6.05	47.2

$AUC_{ss\ (0\text{-}tau)}$(ng.hr/ml)	36	648	37.0	682	221	1300
CL/F (L/hr)	36	1.54	37.0	1.47	0.771	4.53
V_z/F (L)	36	98.4	42.6	100	50.7	330

AUC_{ss} Area under the curve at steady state
CL/F Apparent oral clearance
$C_{ss,max}$ Maximum anastrozole plasma concentration at steady-state
$C_{ss,min}$ Minimum anastrozole plasma concentration at steady-state
CV Coefficient of variation (geometric CV presented)
T_{max} Time to reach the maximum anastrozole concentration;
V_z/F Apparent volume of distribution during terminal phase.

There was no effect of age and weight on anastrozole apparent oral clearance, and no effect of age on apparent volume of distribution. However there was an effect of weight on apparent volume of distribution (p=0.03).

Study 0000

This was a population pharmacokinetic sub-study of study 0046, an open-label study of anastrozole in the treatment of precocious puberty in McCune-Albright Syndrome in girls aged 2-10.

For each subject, blood was sampled once 0-2 hours after the first dose of anastrozole, and once again 3-24 hours after the first dose. Two additional samples were collected randomly at any time after 3 months of treatment. The results were analysed with those from study 0001. The resulting model suggests that Cmax and AUC are increased in girls, by 70% and 34 % respectively, but that a dose adjustment in girls is not necessary.

2.3.4 Pharmacodynamics

Study 0001

After 6 months of treatment with anastrozole 1 mg daily, testosterone, FSH, LH increased, oestradiol and SHBG decreased. The CHMP considered that the results in pubertal boys with gynaecomastia are consistent with the known pharmacology of anastrozole.

2.3.5 Clinical efficacy

Main study (0074)

This was a randomised, double-blind, placebo-controlled multicentre trial to assess the safety and efficacy of anastrozole in increasing predicted adult height of adolescent males with growth hormone deficiency.

Inclusion criteria:

- Pubertal boys with genital Tanner stage ≥II (>4ml testicular volume)
- Bone age of ≥11.5 years and < 15 years
- A peak GH response to pharmacological stimuli of ≤10 ng/ml, and either short stature (>2 standard deviations below average, ie, standardised height is less than minus 2.0), or profound growth deceleration (growth velocity ≤ 25% of corresponding chronological age population).
- On stable daily doses of GH for at least 6 months, using average doses of about 0.3 mg/kg.wk
- Stable organic pathology

Exclusion criteria:

- participation in other trials of hormone treatment within 6 months
- longterm medication that impairs growth
- hereditary disease
- moderate to severe scoliosis

Patients received a marketed formulation of Arimidex 1 mg tablet once daily, orally or a matching placebo, in combination with growth hormone (GH). Patients were treated for 36 months or the completion of linear growth (defined as a bone age of ≥ 16 and a growth velocity of < 2cm/year), whichever came first.

The CHMP noted that the study design is appropriate, and that the inclusion/exclusion criteria define an appropriate target population for the proposed indication. Growth hormone (GH) treatment is not generally advocated for stunted growth in pubertal boys or girls due to the lack of a clinical significant increase in height. It is generally assumed that only a few centimetres (cm) can be added to the final height. This is considered not clinically relevant.

Furthermore the CHMP considered that the rationale for the 1 mg can only partly be endorsed. A lower (0.5 mg) dose might be considered as effective as the 1 mg dose for the whole population, with an additional safety benefit. Therefore a starting dose of 0.5 mg with the potential to increase the dose to 1 mg for those patients in which the oestradiol is not sufficiently decreased is not sufficiently elaborated.

Primary endpoints

The primary endpoint of this trial was change in predicted adult height (PAH) defined as PAH at end of therapy minus PAH at baseline. PAH was estimated by the Bayley-Pinneau method. In order to derive PAH, bone age was determined using the Fels method at the Fels Institute (Yellow Springs,

Ohio, USA). Bone age readings were performed by one single experienced reader, blinded to the treatment arm.

Instead of the final height, the MAH's choice is to use the predicted adult height (PAH) as the primary endpoint. Unfortunately this endpoint is considered inadequate by the CHMP, because no prediction model for growth during puberty exists. Treatment should ideally proceed until final height is achieved. Lack of these data interferes with a conclusive assessment of the efficacy, especially in such a small study sample. Therefore, the primary objective of the study should have been (near) final height. The MAH has made a commitment to obtain final adult height data for as many patients as possible.

Bayley-Pinneau is only acceptable, although far from ideal, for studies in prepubertal children but the use in pubertal children this prediction is not validated. Further the Bayley-Pinneau method is based on the assumption that bone maturation is inherently reduced and cannot be corrected by treatment [1]. This is also contradictory to the mode of action of anastrozole. The validity – as well as sensitivity and specificity in this population - of the method in the present indication in pubertal boys is thus not sufficiently substantiated.

Secondary endpoints

- Near adult height (i.e. bone age >= 16 years and a growth rate <= 2cm/year)
- Growth rate (cm/year)
- Change in height in 'standard deviation score' (SDS) (i.e. difference between SDS scores at baseline and at any other given timepoint).
- Change in height by duration of treatment (cm)
- Last measured height (cm)
- Change in weight (kg)
- Change in BMI
- Change in bone age (years)
- Change in Tanner pubertal stage
- Change in plasma conc of IGF-I
- Bone Mineral Density (BMD) at end of therapy and the change in BMD as compared to baseline for both lumbar spine and whole body
- Tolerability and safety endpoints including adverse events, withdrawals, and laboratory data including osteocalcin, bone specific alkaline phosphatase, insulin, glucose, oestradiol and testosterone concentrations.

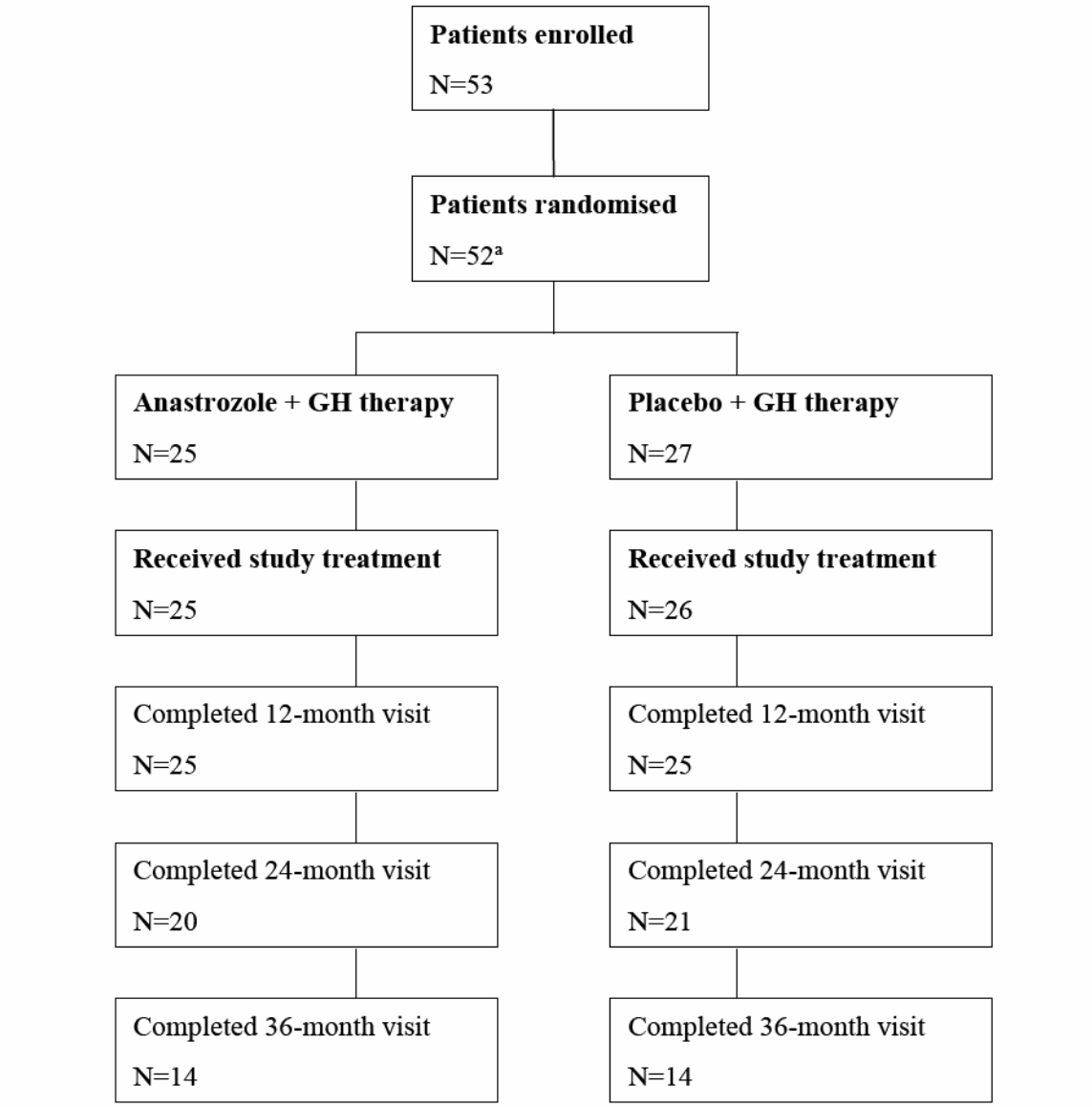
The CHMP noted that all the secondary endpoints are logic and relevant, however, some important endpoints such as height, height SDS (uncorrected), HV SDS, Quality of life, IGF-I and IGFBP-3 are missing.

Treatment arms were compared using ANCOVA adjusting for baseline score, and an unadjusted t-test.

Results

Participant flow is shown in the following flow chart:

[1] Bayley-Pinneau, Roche-Wainer-Thissen, and Tanner height predictions in normal children and in patients with various pathologic conditions Zachmann M, Sobradillo B, Frank M, Frisch H, Prader A. , J Pediatr. 1978 Nov;93(5):749-55



[a]Patient 08OKS0040 was initially randomised to receive anastrozole treatment but was immediately lost to follow-up without receiving study or drug or contributing baseline data. The patient was not included in the main analysis at 3 years but was included in the summary of AEs

Of the 24 patients who did not complete 36 months of treatment, 9 withdrew (attained predefined criteria for completion of linear growth, had psychosocial issues, or were tired of taking the medication) and 5 were discontinued by the investigators (poor drug compliance or lost to follow-up). Of the 5 discontinued, one suffered an AE (psychogenic emesis) that compromised drug compliance. The remaining 10 patients attained pre-defined criteria for final height.

Patients who provided data for some but not all efficacy endpoints at a given study visit were not classified as having completed the study visit. There were no screening failures.

The CHMP is of the opinion that the lack of an acceptable power analysis combined with substantial loss to follow up (up to 45% of the patients) questions the robustness of the study.

Summary of demographic and baseline characteristics**:**

Demographic/Baseline characteristic	**Anastrozole 1 mg**	**Placebo**
Age (years)	N=25	N=27
Mean (sd)	13.76 (1.31)	14.12 (1.13)
Median	13.88	14.20
Range	11.41 to 16.45	11.15 to 16.03
Height (cm)	N=25	N=27
Mean (sd)	149.66 (8.17)	151.63 (6.87)
Median	150.28	151.09
Range	136.69 to 169.88	135.50 to 165.50
BMI (kg/m^2)	N=25	N=26
Mean (sd)	19.95 (3.30)	20.35 (3.76)
Median	18.67	19.49
Range	15.40 to 27.40	15.80 to 30.70
Bone age (years)	N=25	N=25
Mean (sd)	13.65 (1.03)	13.39 (1.18)
Median	14.02	13.46
Range	11.84 to 15.05	11.32 to 15.55
Tanner pubertal stage	N=25	N=26
Median	III	III
Range	II-V	II-V
Duration on prior growth hormone therapy (years)	N=26	N=26
Mean (sd)	3.56 (2.98)	2.58 (2.42)
Median	2.40	1.70
Range	0.50 to 10.80	0.60 to 10.00
Whole body BMD Z-score	N=13	N=13
Mean (sd)	-0.49 (1.42)	-0.45 (1.22)
Median	-0.40	-0.04
Range	-2.80 to 1.46	-2.30 to 0.92
Lumbar spine BMD Z-score	N=15	N=14
Mean (sd)	-1.84 (0.71)	-1.83 (1.17)
Median-1.90	-1.90	-2.05
Range	-3.10 to -0.30	-4.40 to 0.87

The mean duration on prior GH therapy was 3.56 years for the anastrozole arm compared to 2.58 for the placebo arm.

Bone age in the anastrozole group is more or less equal to the chronological age, contrary to the control group in which the bone age shows a lack time of about one year. This will have consequences

for the comparison of the BMD Z score. Comparison between both treatment groups will be in favour of the anastrozole treated group.

The primary efficacy endpoint was predicted adult height (cm):

Predicted height (cm)

		anastrozole	placebo
Baseline	n	24	25
	mean (sd)	164.8 (1.5)	169.2 (1.5)
12 months	n	23	25
	mean (sd)	166.4 (1.5)	169.5 (1.4)
24 months	n	20	23
	mean (sd)	168.3 (1.4)	170.7 (1.5)
36 months	n	16	13
	mean (sd)	169.8 (1.6)	169.2 (2.0)

Change from baseline in predicted height (cm)

		anastrozole	placebo	difference	p-value*
12 months	n	23	25		
	mean (sd)	1.29 (0.73)	0.27 (1.00)	1.02	0.421
24 months	n	20	23		
	mean (sd)	4.46 (1.17)	1.06 (1.06)	3.40	0.037
36 months	n	16	13		
	mean (sd)	6.70 (1.37)	0.95 (1.14)	5.75	0.004
Last value on therapy	mean	5.35	2.10	3.25	0.026

* p-values from a two sample t-test

The results of this endpoint are difficult to interpret for two reasons:

i) There is a large baseline imbalance of 4.4 cm.

From the data above it is clear that the larger change from baseline is in the anastrozole group. However at 36 months the two treatment groups are actually very similar in terms of predicted height, and at 12 and 24 months the placebo group is still ahead. So the greater change in baseline for the anastrozole group only serves to compensate for the baseline imbalance.

It seems possible that as the groups are not comparable at baseline there was a different potential for improvement in the two groups – i.e. there was more room for improvement in the anastrozole group and the better change from baseline is only (or partly) a reflection of that rather than being a true treatment effect.

ii) Many subjects do not provide data at all visits, in particular at the 36 month visit.

When randomised subjects are omitted, this introduces a bias into the comparison. To get a valid comparison an attempt must be made to include all subjects. The ‘last value on therapy’ analysis is an attempt to do this. While there is no discussion of whether this is a reasonable approach, it can be seen that it improves the result for placebo while worsening the result for anastrozole, reinforcing concern regarding the validity of the 36 month comparison.

Change from baseline in predicted height (cm) – model adjusted for baseline

		anastrozole	placebo	difference	p-value*
12 months	mean	0.92	0.61	0.30	0.812
24 months	mean	3.59	1.81	1.78	0.278
36 months	mean	6.08	1.71	4.37	0.026
Last value on therapy	mean	4.82	2.60	2.22	0.119

* from analysis of covariance with terms for treatment and baseline

When adjusting for baseline, the results reinforce the concerns stated above. The treatment differences are all much smaller than those seen in the unadjusted analysis and the statistically significant findings are lost, apart from at the 36 month time-point which as noted above is questionable because of the large amount of missing data. The CHMP considered that the data do not provide convincing evidence that anastrozole increases predicted height.

Change from baseline in bone age (years) – model adjusted for baseline

		anastrozole	placebo	difference	p-value*
Baseline	mean	13.65	13.39		
12 months	mean	1.11	1.34	-0.231	0.108
24 months	mean	1.86	2.67	-0.81	<0.001
36 months	mean	2.54	4.03	-1.49	<0.001

* from analysis of covariance with terms for treatment and baseline

Bone age data should be related to GH dose and IGF-I levels, testicular volume or Tanner stage. It is noted that, although there is strong evidence that anastrozole reduces bone ageing, the other secondary endpoints show no evidence of a treatment effect.

Clinical safety

In addition to the safety data submitted as part of the pivotal trial 0074, the applicant has also submitted safety data from 4 additional studies. These study populations are summarised in the following table:

Study	**Design**	**Condition**	**Gender**	**Age range**
0001	Open-label	Pubertal gynaecomastia	Male	10-17
0006	Placebo-controlled	Pubertal gynaecomastia	Male	11-18
0046	Open-label	McCune-Albright syndrome	Female	2-10
0047	Open-label	Testotoxicosis	Male	2-9

Although the study populations differ from the target population for the proposed indication, the additional safety data are considered relevant.

Patient exposure

The following table summarises exposure for all submitted studies:

Exposure	**Study**					
	0074 (pivotal)	**0001**	**0006**	**0046**	**0047**	
Anastrozole dose	1 mg	1 mg	1 mg	1 mg	0.5 mg	1 mg
Patients enrolled	26	38	82	28	10	4
Total patients exposed	25	38	43	28	10	4
Mean exposure (days)	Not available	166	182	355	340	
Patients exposed ≤ 6 months	0	38	43	1	0	1
Patients exposed > 6 months ≤ 12 months	0	0	0	27	10	3
Patients exposed > 12 months ≤ 24 months	5	0	0	0	0	0
Patients exposed > 24 months < 36 months	6	0	0	0	0	0
Patients exposed 36 months	14	0	0	0	0	0

It is noted that mean exposure data were not available for the pivotal study (0074).

Adverse events

In the main study (0074), fractures occurred more commonly in the anastrozole arm. Eight fractures were reported by 6 patients (23.1%) in the anastrozole arm, compared to 2 fractures reported by 2 patients (7.4%) in the placebo arm. Four fractures in the anastrozole arm (including 3 in one patient) were due to sporting injuries.

Summary of fractures by preferred term:

MedDRA PT	Number (%) of patients	
	Anastrozole	Placebo
	N=26	N=27
Foot fracture	2 (7.7)	0
Hand fracture	2 (7.7)	1 (3.7)
Ankle fracture	1 (3.9)	1 (3.7)
Avulsion fracture	1 (3.9)	0
Pelvic fracture	1 (3.9)	0
Upper limb	1 (3.9)	0

In study 0046, 3 out of 28 patients (10.7%) reported a fracture during the 12 months of anastrozole treatment, 2 of whom had a history of fibrous dysplasia of bone. In study 0006, a fracture occurred in the anastrozole arm (fractured thumb).

The excess of fractures in the anastrozole group, from the main pivotal study 0074, is concerning. The applicant has provided further detail regarding fractures in studies 0074 and 0046. The applicant states that 5 patients in the anastrozole arm of 0074 reported 8 fracture events compared to 2 patients reporting 2 fracture events in the placebo arm. Having re-examined the data, it appears that in study 0074, 6 patients in the anastrozole arm reported 8 fractures. The applicant has agreed to add wording to section 5.1 of the SPC, to reflect the apparent increased rate of fracture in the anastrozole arm of 0074 (see section 2.4).

The other adverse events were consistent with the known adverse effects of anastrozole in postmenopausal women with breast cancer, or were characteristic of the paediatric populations studied.

Serious adverse events and deaths

In the main study 0074, there were a total of 7 SAEs reported by 4 patients in the anastrozole group. None were judged by the investigator to be causally related to the study treatment. There were no SAEs in the placebo arm. No deaths were reported in any of the studies submitted.

Laboratory and physical examination findings

In the main study (0074), oestradiol levels were lower in the anastrozole group, compared to placebo, at 12, 18, 24, 30 and 36 months. Levels of testosterone, IGF-I, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, osteocalcin and glucose were similar in both treatment groups for the majority of the visits. No significant abnormalities of full blood count or liver function tests were reported. Body mass index increased during the treatment period in both arms with no significant differences. There was a trend towards lower % body fat in the anastrozole group. Tanner pubertal stage steadily increased in both treatment groups at each timepoint. There were no treatment differences.

Safety outcomes measures, including Tanner staging, hormone levels and liver function tests were consistent with the findings of the main study 0074.

Increases in plasma concentration of IGF-I compared to baseline were seen in both treatment arms. The ANCOVA analysis of change from baseline in plasma concentration of IGF-I indicated that at 18 months the increase vs baseline was significantly larger in the anastrozole treatment arm, compared to the increase vs baseline in the placebo treatment arm. However, the change from baseline in IGF-I concentration was similar between the 2 treatment arms at the other study time points. The increase in

IGF-I strongly suggests a recent start of the GH treatment. Therefore it cannot be considered that these patients are on stable GH treatment. This hampers the assessment of the effect of anastrozole in this group. It is interesting to see a difference in the IGF-I concentration between both treatment groups, for the IGF-I concentration is clinical practice used to titrated the GH dose. Apparently some differences in treatment with GH occurred during the study. This imbalance will hamper the assessment for concomitant treatment appears to be different between both groups.

Radiological findings

BMD data was only available for the main study (0074):

Whole body bone mineral density z-score

		anastrozole	placebo	p-value
Baseline	n	13	13	
	mean (sd)	-0.49 (0.39)	-0.45 (0.34)	
24 months	n	13	13	
	mean (sd)	-0.42 (0.31)	-0.11 (0.19)	0.394
	adjusted for baseline	-0.41	-0.12	0.233
36 months	n	6	5	
	mean (sd)	-0.49 (0.26)	-0.24 (0.43)	0.618
	adjusted for baseline	-0.54	-0.18	0.380

The z-score is a measure of how far the BMD varies from the average age-related population. The negative values indicate that the study subjects had lower than average BMD. While the anastrozole patients stayed low, there was a sign that the subjects on placebo were returning towards normal levels.

The data on this endpoint is far too small to draw any firm conclusions, and accordingly there are no significant p-values. However the existing data are not reassuring and it is not possible to rule out a negative influence of anastrozole.

Lumbar spine bone mineral density z-score

		anastrozole	placebo	p-value
Baseline	n	15	14	
	mean (sd)	-1.84 (0.18)	-1.83 (0.31)	
24 months	n	15	12	
	mean (sd)	-1.56 (0.17)	-0.98 (0.32)	0.101
	adjusted for baseline	-1.54	-1.00	0.009
36 months	n	8	9	
	mean (sd)	-1.16 (0.32)	-0.75 (0.35)	0.404
	adjusted for baseline	-1.18	-0.74	0.253

BMD data was not collected in the supporting studies submitted.

Lumbar spine BMD results are similar to those seen for whole body BMD. There are not enough data for firm conclusion to be drawn, but the signals are concerning. Additional wording to this regard has been proposed to section 5.1 of the SPC (see section 2.4).

Discontinuation due to AES

The discontinuations in all studies were unremarkable, and not judged causally related to study treatment.

2.4 *Changes to the product information*

Having decided not to further pursuit the request for an extension of indication, the MAH presented a proposal to update the Product Information with relevant paediatric information as foreseen under Article 36 of Regulation (EC) No 1901/2006. The agreed additions to the SPC are detailed in appendix 1. No changes to the Package Leaflet are required at this time, as the MAH confirmed that the statement '*Arimidex should not be given to children*' (or a similar one) is already included in the Product Information of the Member States. The only exception is Latvia, where a variation to insert the statement has been submitted and is currently pending approval.

2.5 *Pharmacovigilance*

2.5.1 Risk Management Plan (RMP)

The Applicant has submitted a consolidated version of a RMP for Arimidex (version dated 14 July 2009). This document was updated to include the information arising from the paediatric studies, and the same modifications should be introduced to all local Risk Management Plans.

The CHMP, having considered the data submitted in the application, is of the opinion that the following actions are required with regards to the local risk management plans, in order to ensure the safe and effective use of the medicinal product:

Table Summary of the requirements related to the local risk management plans

Section		**Changes to be introduced**
Safety Specification		
	1.1 Non-clinical	Change of title from *infertility in paediatric males* to *Relevant data from reproductive toxicity studies*. Additional information on the rat fertility study should be included.
	1.2 Clinical safety	The statement on paediatric clinical trials should read *Arimidex is not indicated for use in children as safety and efficacy have not been established in the paediatric populations studied*.
	1.2.2 Populations not studied in the pre-authorisation phase	Add *Girls with short stature due to growth hormone deficiency have not been investigated in clinical studies.*
	1.2.4.1 Important identified risks	The following information should be added: A*rimidex is known to be associated with joint pain and stiffness and all patients, including the paediatric population, may be at risk. However, post-menopausal women are most at risk due to low circulatory levels of oestrogen.*
	1.2.4.3 Important potential risks	A potential risk designated as *infertility in paediatric males* should be renamed as *Risk of infertility and possible embryotoxicity following treatment of pubertal boys.*
	1.4 Epidemiology of the indication(s) and important events	No information on paediatric use should be included as this section is related to the therapeutic indication.

	1.6.1 Potential for off-label use	The following information should be added on potential off-label use: *<u>Potential off-label use for paediatric patient populations which have been investigated in clinical trials</u>* *There is the potential for ARIMIDEX to be used off-label for pubertal boys with short stature due to growth hormone deficiency, for gynaecomastia or for testotoxicoses as well as in girls with McCune-Albright Syndrome.* *<u>Potential off-label use for paediatric patient populations which have not been investigated in clinical trials</u>* *There is the potential for ARIMIDEX to be used off-label for girls with short stature due to growth hormone deficiency.* *The efficacy and safety of anastrozole was not investigated in girls with GHD on the grounds of a potential safety concern that means the benefit risk assessment in girls with GHD is not considered favourable. Increased risk of ovarian cyst formation and development of ovarian torsion has been reported in premenopausal women treated with AIs; the use of an AI in prepubertal and pubertal girls may carry the same risk. It is hypothesised that the low circulating concentrations of oestrogen following the administration of an AI could lead to increased concentrations of gonadotropins, increasing the risk of cyst formation and ovarian torsion. Evidence to support this hypothesis comes from non-clinical studies:* • *In an anastrozole 2 year oncogenicity study (Study TCR/2448) the ovaries of rats dosed with 1, 5 or 25 mg/kg/day showed some increase in follicular cysts, a reduction in the number of corpora lutea and follicles, and hyperplasia of the stroma.* • *In a separate anastrozole 2 year oncogenicity study (Study TCM/895) the ovaries of mice dosed with 5, 15 or 50 mg/kg/day showed a diffuse sex cord stromal hyperplasia with an increased incidence of haemocysts and haemosiderin (brown) pigment. The incidence of cysts (simple cysts lined by a flat epithelium) and cystic/papillary hyperplasia (cysts lined by a cuboidal or columnar epithelium often showing some papillary infolding) was also disturbed, with the greatest incidence in the low dose group.* • *In rats, administration of letrozole at doses up to 1 mg/kg for 21 days resulted in a high incidence of subcapsular ovarian cysts and capsular thickening together with incomplete luteinisation and a decreased number of corpora lutea.* *AstraZeneca has received 20 reports, from AstraZeneca sponsored clinical studies, unsponsored clinical studies and spontaneous sources, of paediatric use of ARIMIDEX up to 11 August 2008. Reasons for use include: breast cancer, McCune Albright syndrome, gynaecomastia, precocious puberty, adrenogenital syndrome, growth retardation and blood growth hormone increased. There was no clustering of adverse events observed. Limited safety data from studies of ARIMIDEX in paediatric populations suggest the safety profile in paediatric patients is generally consistent with the known safety profile of ARIMIDEX 1 mg in the adult population.* *Section 5.1 of the current SmPC for ARIMIDEX states: 'Arimidex is not indicated for use in children. Efficacy has not been established in the pediatric populations studied. Although the overall assessment of adverse events in children less than 18 years raised no safety or tolerability concerns, the number of children treated was too limited to draw any reliable conclusions. No data on the potential long-term effects of anastrozole treatment in children are available.'*
	1.7 Summary of ongoing safety concerns	*Use in male patients for the treatment of Gynaecomastia* and *Possible effects on Bone Mineral Density in paediatric patients* to be removed from this section.
Pharmacovigilance Plan		
	2.2 Summary of planned pharmacovigilance actions	Information on use in paediatric males for gynaecomastia, testotoxicosis and short stature due to hormone growth deficiency, and use in paediatric females for McCune-Albright Syndrome and short stature due to growth hormone e deficiency should be removed from the section *Important missing information* and inserted under *off-label use*.
		The safety concern *infertility in male paediatric patients* should be reworded to *risk of infertility and possible embryotoxicity following treatment of pubertal boys*.
Evaluation of the need for risk minimisation activities		
		Information on use in paediatric males for gynaecomastia, testotoxicosis and short stature due to hormone growth deficiency, and use in paediatric females for McCune-Albright Syndrome and short stature due to growth hormone e deficiency should be removed from the section *Important missing information* and inserted under *off-label use*. Activities should include: • Use of the SPC to emphasise that Arimidex is not recommended for use in

		children due to insufficient data on safety and efficacy • Routine pharmacovigilance activities • Revision of the topic in PSURs in line with the current requirements for the section concerning children.
		The safety concern *infertility in male paediatric patients* should be reworded to *risk of infertility and possible embryotoxicity following treatment of pubertal boys.*

2.6 Benefit Risk Assessment

Following assessment of the documentation submitted, the benefit risk balance for the proposed indication 'treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone' was considered negative for the following reasons:

- There are non-clinical concerns regarding fertility and embryotoxicity, which may be of clinical relevance
- While there may be some evidence of efficacy in relation to bone age, there is no convincing evidence that this would be translated into a meaningful benefit in terms of final adult
- Additionally no final height data has been made available
- Clinical evidence suggests that anastrozole may adversely affect bone mineral density

The possible clinical benefit is outweighed by unresolved safety concerns in relation to bone mineral density, fracture rate, male fertility, embryotoxicity and carcinogenicity.

3 Overall conclusions and Recommendations

The CHMP is of the opinion that studies D5390L00074 and D6873C00047, which are contained in the agreed Paediatric Investigation Plan and have been completed after 26 January 2007, are considered as significant.

Based on the CHMP review of data on safety and efficacy, the CHMP considered that the risk benefit balance of Arimidex 1mg film-coated tablets in the treatment of short stature in pubertal boys with growth hormone deficiency, in combination with exogenous growth hormone, was unfavourable and therefore did not recommend the granting of an extension of the Marketing Authorisation.

Furthermore, the CHMP took note that the PDCO adopted on 3 April 2009 an Opinion on Compliance (see attachment 9) with the agreed PIP (Decision P/20/2009 adopted on 6 February 2009, see attachment 10) under Article 23 of Regulation EC (No) 1901/2006, as amended, for the above mentioned product and that the PDCO concluded in accordance with Article 28(3) and Article 45(3) of the said Regulation that the development of this product has complied with all measures in the agreed PIP.

For the purpose of the application of the Article 45(3) of Regulation EC (No) 1901/2006, significant studies in the agreed paediatric investigation plan have been completed after the entry into force of that Regulation.

Furthermore, the Committee is of the opinion that the MAH, having decided not to further pursue the above mentioned indication, has adequately reflected the results of the paediatric studies in the Summary of Product Characteristics.

3.1 Commitments to be fulfilled by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to comply with the commitments listed below:

Commitments
AstraZeneca AB commits to submit an RMP or its update at national level for Arimidex taking into account the new paediatric data and the CHMP recommendations.
AstraZeneca AB commits to ensure that the Package Leaflet in all languages contains a statement referring to the fact that Arimidex should not be given to children.