Table 74. Treatment-Related Allergic-Type Skin Disorders Through Day 169 (Studies 149-98-02, 149-98-03, and 149-99-03)

Preferred Term	Lupron N = 284 n (%)	Lupron Plus Casodex N = 83 n (%)	Abarelix N = 735 n (%)
Rash[1]	3 (1)	3 (4)	19 (3)
Pruritus	5 (2)	1 (1)	15 (2)
Urticaria[2]	2 (1)	0	2 (< 1)
Dermatitis	0	0	2 (< 1)
Eczema	0	0	0
Overall[3]	10 (4)	4 (5)	36 (5)

[1] Rash, erythematous rash, maculopapular rash
[2] Urticaria and acute urticaria
[3] Total number (percentage) of patients with any allergic-type skin disorder. Patients with multiple events were counted once.
Source: Table 6-H, pg 50, Safety Update, Submission of March 2001.

Medical Officer's Comment

- *The percentage of patients exhibiting these "allergic" cutaneous disorders was similar in the 3 treatment groups. Allergic cutaneous disorders do not, in general, represent a serious safety concern if they (a) are not accompanied by other systemic changes such as hypotension, syncope, or respiratory distress and (b) do not initially occur within 1-2 hours of dosing. Some of the patients in the abarelix group exhibited one or more of these symptoms of a more serious reaction and are reviewed in the following section.*

7.16.2 Systemic Allergic Reactions

7.16.2.1 Allergic Reactions for Which Patients Were Withdrawn from the Clinical Trials or Which Occurred Immediately (within One Hour) Postdosing (FDA Analysis)

A total of 23 patients participating in the abarelix clinical development program were either withdrawn because of an allergic type of reaction (n=21), experienced an immediate post-dosing hypotensive reaction, classified as a vasovagal reaction by the investigator but indistinguishable from an immediate systemic allergic reaction, that led to withdrawal (n=1), or experienced an immediate post dosing allergic reaction but continued treatment without further sequelae (n=1). Twenty (20) of these 23 patients were treated with abarelix. Table 75 lists for each of these patients the following information: treatment assignment, time of onset of adverse reaction relative to dosing, and whether the reaction included hypotension and/or syncope.

Table 75. Patients Withdrawn from Clinical Trials due to an Allergic Reaction or with an Immediate Post Dosing Systemic Reaction [1]

Study Number	Patient Number	Treatment	Time of Reaction (Onset After Dosing)	Syncope or Hypotension
Onset of adverse reaction within 1 hour of dosing				
149-97-04	02-4635	Abarelix	2 min	No
149-98-02	11-2218	Abarelix	5 min	No
149-98-03	16-3028 [1]	Abarelix	5 min	No [1]
149-98-03	76-3224	Abarelix	Immediate	No
149-98-03	09-3246	Abarelix	<15 min	No
149-98-04	401-4001	Abarelix	Immediate	Yes
149-98-04	409-4057	Abarelix	Immediate	No
149-98-04	416-4067	Abarelix	5 min	No
149-99-03	357-2226	Abarelix	45 min	No
149-99-03	313-3087	Abarelix	<10 min	Yes
149-99-03	333-3336 [2]	Abarelix	Immediate	Yes [2]
149-99-04	01-2192	Abarelix	5 min	Yes
ABACAS 1	14070281	Abarelix	Immediate	Yes
ABACAS 1 Extens.	29419985	Abarelix	5 min	Yes
ABACAS 1 Extens.	26860319	Abarelix	2 min	Yes
—	NP [4]	Abarelix	15 min	No
Onset of adverse reaction more than 1 hour after dosing				
149-97-04	38-4700	Abarelix	5 days	No
149-98-02	13-2144	Lupron	5 days	No
149-98-03	27-3200	Abarelix	2 hrs (approx.)	No
149-99-03	301-1295	Lupron	6 days	No
ABACAS	21540077	Abarelix	1 day	No
ABACAS	7450299	Zoladex	10 days	No
— [3]	NP [4]	Abarelix	8 hrs	No

[1] All patients were withdrawn except for Patient 16-3028.
[2] Investigator classified event as a severe vasovagal reaction with unknown association to study drug.
[3] Investigator-initiated study by Dr.
[4] Not provided.
Source: Tables 6-I, 6-U and pg 105 and 114 of Safety Update (Submission of March 2001), Supplemental Safety Submission of 6 April 2001, CIOMS Reports for ABACAS 1, and Submission of 8 May 2003, pg 189-199.

Sixteen (16) of the 23 reactions (all in the abarelix group) occurred within 1 hour of dosing. Fifteen (15) of these 16 reactions occurred within 15 minutes of dosing. Allergic signs or symptoms in 7 of the 23 patients included loss of consciousness and or hypotension. These latter 7 reactions all occurred in patients receiving abarelix and all occurred within 10 minutes of dosing.

Medical Officer's Comment

- *The clinical presentations of the immediate systemic reactions in at least 16 of the 20 patients receiving abarelix are clearly different than those observed in patients receiving Lupron or Zoladex. These 16 reactions occurred within 1 hour of dosing while the 3 reactions in patients receiving Lupron or Zoladex occurred several days after dosing. The clinical presentation of the immediate reactions (i.e., those within 1 hr of dosing) in the abarelix group suggests that patients experienced an acute release of histamine or other vasoactive substance (i.e., an anaphylactoid or anaphylactic type of reaction).*

All patients recovered without sequelae. Management ranged from no treatment in 6 of the 16 patients with an immediate allergic reaction to aggressive therapy that included oxygen, IV fluid, epinephrine, Benadryl, Solumedrol and albuterol in 1 patient. One patient (No. 16-3028) who experienced generalized warmth, tingling, pruritus, and erythema (but no syncope or hypotension) 5 minutes after his 8th dose of abarelix continued dosing without any subsequent allergic events and completed the study. More detailed information about each of these patients is provided in Table 76.

APPEARS THIS WAY
ON ORIGINAL

Table 76. Patients Withdrawn Due to a Drug-Related Allergic-Type Reaction or With an Immediate Post Dosing Systemic Reaction

Patient No.	Study No.	Rx[1]	Adverse Event (Description)	Dose No. & Study Day of Dosing		Onset of AE After Dosing	Rx of AE	Time of AE Resolution	Withdrawn Yes/no
02-4635	149-97-04	A	Facial flushing	--	Day 676	2 min	None	30 min	Yes
38-4700	149-97-04	A	Pruritus & rash	25	Day 645	5 days	Benadryl, Topical HC		Yes
13-2144	149-98-02	L	Pruritus, urticaria, & maculopapular lesions	1	Day 1	5 days	Benadryl po	5 days	Yes
11-2218	149-98-02	A	Flushing of neck, head, ears; Diffuse erythematous rash with burning and pruritus	2	Day 15	5 min	Medrol x 6 d	6-7 hrs	Yes
16-3028	149-98-03	A	Generalized warmth, tingling, pruritus, erythema, [drug continued without recurrence]	8	Day 169	5 min	None	Same day	No
27-3200	149-98-03	A	Urticaria	9	Day 197	2 hrs	None	NI[2]	Yes
09-3246	149-98-03	A	Warm sensation in neck Pruritus & urticaria of trunk, neck, face; had RCM[3] 2 hr predosing	5	Day 85	Warmth: Immediately; urticaria: 15 min	None	Itching: 30 min; Urticaria: 1 hr	Yes
76-3224	149-98-03	A	Urticaria of legs; Pruritus of hands; tingling of extremities, Palpitations	3	Day 29	Immediately	None	1 day	Yes
357-2226	149-99-03	A	Generalized rash	5	Day 85	45 min	Benadryl	1 day	Yes
401-4001	149-98-04	A	**Loss of consciousness;** Generalized erythematous rash; **Hypotension;** Edema of ankles wrists, lips, and periorbital area,	7	Day 141	Immediately	Oxygen, IV fluids, Epinephrine, Benadryl, Solumedrol, Albuterol,	4 hrs	Yes
409-4057	149-98-04	A	Warm neck, Urticaria & pruritus of upper back, neck, chest	3	Day 29	Immediately	None	Same day	Yes
416-4067	149-98-04	A	Urticaria	2	Day 15	5 min	Benadryl	Same day	Yes
301-1295	149-99-03	L	Numbness & swelling lower lip Muscle tightness hands Red patches on palms	3	Day 57	6 days	Epinephrine Benadryl Prednisone Cetirizine,	12 days	Yes

[1] L = Lupron, A = abarelix.
[2] NP = Not provided.
[3] RCM = Radiocontrast media.

(continued)

Table 76 Patients Withdrawn Due to a Drug-Related Allergic-Type Reaction or with an Immediate Post Dosing Systemic Reaction (cont.)

Patient No.	Study No.	Rx[1]	Adverse Event (Description)	Dose No. & Study Day of Dosing		Onset of AE After Dosing	Rx of AE	Time of AE Resolution	Withdrawn Yes/no
313-3087	149-99-03	A	Nausea; Ringing/itching of ears; **Orthostatic hypotension**; **Unresponsive**; incontinent; Flushing of face, chest, & abd; diaphoretic	4	Day 57	< 10 min	Elevate leg Nasal O_2 IV Fluids	40 min	Yes
333-3336	149-99-03	A	Tingling fingertips, felt hot: Labored breathing; **Syncope,** incontinence, **hypotension;** Received RCM[4] earlier in day	2	Day 16	Immediately	IV fluids	3 hours	Yes [2]
01-2192	149-99-04	A	**Unresponsive with rapid respiration;** BP of 106/70; Flushed appearance; followed by erythematous rash.		Day 617	5 min	SC Benadryl Oxygen		Yes
7450299	ABACAS 1	Z	Rash, pruritus on neck and ears	2	Day 29	10 days	None	NI [3]	Yes
14070281	ABACAS 1	A	Face red & hot; **Hypotension (80/50),** Diffuse rash Blood tryptase 1.5 x ULN 2 hr post dose	1	Day 1	Immediately	Clemastine IV	1 hr	Yes
21540077	ABACAS 1	A	Cutaneous erythema, itching on extremities	9	Day 229	One day after	NI [3]	NI [3]	Yes
26860310	ABACAS 1 Extension	A	Hot flushes and dysaesthesia; **Syncope** and urinary incontinence; **Hypotension (88/33)**	23	Day 589	2 min	IV Hydrocort. Fluids	NI [3] Discharged 3 days later	Yes
29419985	ABACAS 1 Extension	A	Felt warm with red face and chest; **Hypotension (82/50);** Generalized pruritus	15	Day 365	5 min	Clemastine IV Hospitalized for 24 hr	Within 1 hr	Yes
NP[3]	—	A	Itching, flushing, and hives	4	Day 56	15 min	Antihistamine Steroids	Within 1 hr	Yes
NP[3]	—	A	Swelling of face, chin, and forearm	1	Day 1	8 hr	Benadryl	NI [3]	Yes

[1] L = leuprolide depot, A = abarelix depot, Z = Zoladex plus Casodex.
[2] Investigator called event vasovagal reaction of unknown etiology;
[3] NP = Not provided; [4] RCM = Radiocontrast media; [5] Investigator initiated study by Dr.
Source: Same as Table 75.

One immediate allergic reaction that included the development of hypotension (Patient 14070281, ABACAS 1) occurred immediately after the first dose of abarelix. The distribution of the 16 reactions that occurred within 1 hour of dosing, relative to the total number of doses that the patient had received, is provided in Table 77.

Table 77 Dose After Which Systemic Allergic Reaction Occurred (Reactions Within 1 Hr of Dosing)

Dose Number	Number of Patients Affected
1	1
2	3
3	2
4	2
5	2
6 to 10	2
> 10	4

Source: Table 76 of this review.

Medical Officer's Comments

- *Immediate allergic reactions occurred throughout the treatment period ranging from immediately after first dosing to as late as Study Day 676. The wide distribution of allergic reactions relative to the onset of first dosing does not clarify if the reactions are likely to be anaphylactoid (direct pharmacological effect of abarelix causing release of histamine) or anaphylactic (IgE mediated reaction against abarelix, an abarelix complex, or an excipient such as carboxymethylcellulose). The distribution of reactions suggests that both mechanisms may be involved.*
- *After the original NDA received a Not Approvable Action, the Sponsor conducted additional immunologic analyses, including screening for the presence of IgE antibodies to abarelix or other components in the final drug product (see Section 7.16.2.4) in an effort to elucidate the mechanism(s) of these allergic reactions.*

7.16.2.2 Incidence and Cumulative Rate of Systemic Allergic Reactions (FDA Analyses)

Proportion of patients experiencing a systemic allergic reaction

The percentages of patients in the abarelix and active control treatment groups that experienced allergic reactions that (a) occurred within 1 hr post dosing or (b) resulted in withdrawal of the patient from the clinical trial is presented in Table 78 (calculations performed by Medical Reviewer).

Abarelix Group. Twenty (20) of 1,414 patients treated with abarelix (1.41% of patients) experienced an allergic reaction that either occurred within 1 hr post dosing or resulted in withdrawal from the clinical trial. Of these cases of allergic reaction, 16 (1.13% of patients) occurred within 1 hour of dosing. In 7 patients (0.50% of patients), the allergic reaction included syncope and/or hypotension.

Active Control Groups. Three of 484 patients treated with Lupron or Zoladex (0.7% of patients) experienced an allergic reactions that resulted in their withdrawal from the clinical trial. None of the reactions occurred within 1 hour of dosing (i.e., there were no immediate allergic reactions), and none of the allergic reactions included syncope or hypotension.

Table 78. Percentage of Patients Experiencing Systemic Allergic Reactions (FDA Analysis)

Treatment Group	Treated Patients N	Had Systemic Reaction n (%) [6]	Had Immediate Reaction (<1 hr) n (%) [6]	Had Syncope or Hypotension n (%) [6]
Abarelix	1414[5]	20[1] (1.41%)[2]	16[3] (1.13%)	7[4] (0.50%)
Lupron or Zoladex	484	3 (0.62%)	0	0

[1] Event in 1 patient (333-3336) called "severe vasovagal reaction" with unknown association to study drug by Investigator. Event in 1 patient (16-3028) did not result in withdrawal of patient from clinical trial.
[2] Elimination of these 2 patients reduces the percentage to 1.27%.
[3] Includes patients 333-3336 and 16-3028.
[4] Includes patient 333-3336. Exclusion of this patient reduces the percentage to 0.4%
[5] Includes 17 patients from Investigator initiated study of
[6] Calculations performed by Medical Reviewer,
Source: Submission of 8 May 2003 (Table 9-3); Submission of 25 February 2003 (Vol. 17 [ISS] pg 239; and Table 75 of this review.

Life table (Kaplan Meier) analysis of immediate systemic allergic reactions

To determine if the rate of immediate systemic allergic reactions in abarelix-treated patients changed across time with duration of dosing, the FDA biostatistician (Kate Meaker), performed a life table (Kaplan Meier) analysis of the incidence rate of immediate allergic-type reactions. The results of this life table analysis are presented in Table 79. The one-year cumulative event rate using the life table method was estimated to be 1.24%, with a 95% two-sided confidence interval of (0.43%, 2.04%). The rate increased after one year, to 2.91% (0.87%, 4.95%) by Day 676. The overall event rate was 1.07% (0.60%, 1.76%).

Table 79 Life Table Analysis of Immediate-Onset Allergic Reactions

Treatment Duration (Days)	Number of Patients with Reaction [1]	Number of Patients Remaining [1]	Allergic Reaction Event Rate (%)	95% Confidence Interval on Event Rate (%)	
0	0	1397	0.00	0.00	0.00
1	1	1396	0.07	0.00	0.21
15	3	1394	0.21	0.00	0.46
16	4	1393	0.29	0.01	0.57
29	6	1366	0.43	0.09	0.78
56	7	1317	0.51	0.13	0.88
85	9	1063	0.69	0.24	1.14
141	10	952	0.80	0.30	1.29
196	11	603	0.95	0.37	1.54
365	*12*	*340*	*1.24* [2]	*0.43*	*2.04*
589	13	187	1.76	0.46	3.05
617	14	179	2.30	0.63	3.96
676	15	159	2.91	0.87	4.95
Overall Event Rate	*15*	*1397*	*1.07%*	*0.60%*	*1.76%*

[1] The analysis does not include the 17 patients in clinical trial and the 1 patient among these 17 who had an allergic reaction within 1 hr of dosing. Therefore, in the life table analysis, the number of patients at risk is 1397, and the total number of reactions is 15 in this analysis.
[2] Rate at 1 year.
Source: Biostatistical Review of NDA 21-320, July 25, 2003, Table 1.

A second life table (Kaplan Meier) analysis to determine the rate of immediate allergic reactions that included syncope and/or hypotension also was performed. The results of this life table analysis are presented in Table 80. The one-year cumulative event rate using the life table method was estimated

to be 0.61%, with a 95% two-sided confidence interval of (0.00%, 1.24%). The rate increased after one year, to 1.67% (0.07%, 3.28%) by Day 617. The overall event rate was 0.50% (0.20%, 1.03%).

Table 80 Life Table Analysis of Immediate-Onset Allergic Reactions with Syncope and/or Hypotension

Treatment Duration (Days)	Number of Patients with Reaction [1]	Number of Patients Remaining [1]	Allergic Reaction Event Rate (%)	95% Confidence Interval on Event Rate (%)	
0	0	1397	0.00	0.00	0.00
1	1	1396	0.07	0.00	0.21
16	2	1395	0.14	0.00	0.34
56	3	1317	0.22	0.00	0.46
141	4	952	0.32	0.00	0.64
365	*5*	*340*	*0.61* [2]	*0.00*	*1.24*
589	6	187	1.13	0.00	2.34
617	7	179	1.67	0.07	3.28
Overall Event Rate	*7*	*1397*	*0.50%*	*0.20%*	*1.03%*

[1] The analysis does not include the 17 patients in clinical trial, none of whom had an immediate systemic allergic reaction that include syncope or hypotension. Therefore, the number of patients at risk is 1397 in this analysis.
[2] Rate at 1 year.
Source: Biostatistical Review of NDA 21-320, July 25, 2003, Table 2.

Medical Officer's Comments

- *Based on the life table analyses, the likelihood of a patient experiencing an allergic reaction within 1 hour of dosing (with or without syncope and/or hypotension) increases with duration of dosing. However, from these analyses it is not clear if the increase is due only to the cumulative risk of repeated dosing or exceeds that of the cumulative risk.*

7.16.2.3 Incidence of Systemic Allergic Reactions (Sponsor's Analyses)

The Sponsor, in the submission of 25 February 2003 (ISS, Vol. 17, pg 189-199) and the response of 8 May 2003 (pg 195-199) to a request for additional information concerning systemic allergic reactions, presented an alternative analysis of the relative likelihood of a patient experiencing a systemic allergic reaction in the abarelix or Lupron/ Zoladex treatment groups (Table 81). The sponsor argued that the risk of an allergic reaction should be consider in terms of patient-years of exposure to Study Drug or proportion of injections associated with an allergic reaction. The Sponsor also presented supplemental analyses in the Submission of 4 November 2003 that challenged the FDA assertion that the increased risk of an allergic reaction with duration of dosing exceeded that of the expected cumulative risk.

Table 81. Patient Withdrawals due to Allergic-Type Signs/Symptoms or Allergic Reactions (Sponsor's Analysis)

	Lupron or Zoladex N = 484	Abarelix N = 1397
Number of patients withdrawn due to an allergic adverse event	3	17 [1]
Number of patients with an immediate onset systemic allergic event [2]	0	6 [2]
Total number of patient years of exposure	291.4 yr	1117.1 yr
Proportion of patients withdrawn due to an allergic event	0.62%	1.22%
Number of patients withdrawn due to an allergic event per 100 patient-years of exposure	1.03 pts	1.52 pts
Proportion of patients withdrawn due to an immediate onset systemic allergic event	0%	0.43%
Proportion of injections associated with an immediate onset systemic allergic event	0%	0.04%

[1] The sponsor's analysis did not consider patient 333-3336 or 16-3028 as having had a systemic allergic reaction, nor did it include the 2 patients with allergic reactions in the investigator-initiated study of
[2] Includes only patients who had syncope or hypotension; does not include patient 333-3336.
Source: Submission of 8 May 2003, Table 9-4, pg 198.

Medical Officer's Comment

- *The Sponsor's argument that patient exposure years should be used to assess the relative likelihood of a patients experiencing an allergic reaction has merit; however, since no patients in the Lupron/ Zoladex groups experienced an allergic reaction that occurred within 1 hour of dosing or that involved loss of consciousness or hypotension, the manner by which risk is calculated (simple proportions, patients years of exposure, or per injection) is of less importance than the nature or severity of the reactions in the abarelix-treated patients.*
- *There are two critical differences between the allergic reactions in the abarelix group and the active control groups: (1) there were no reactions in the active control groups with an immediate onset but there were such reactions in the abarelix group; and (2) there were no reactions in the active control groups associated with hypotension or syncope but there were such reactions in the abarelix group. The Sponsor's analysis of the risk associated with abarelix treatment minimizes these differences.*
- *The Sponsor's overall analysis and risk-benefit analysis also minimizes the clinical importance of allergic reactions that included the immediate onset (within 1 hr of dosing) of flushing, erythema, rash, urticaria, or pruritus without hypotension or syncope. Excluding this group is not appropriate. These reactions are likely to have resulted from the same mechanism, but of a lesser severity, as those associated with hypotension and/or syncope.*

7.16.2.4 Additional Immunologic Studies to Investigate the Etiology of Immediate Systemic Allergic Reactions

The design of these studies and the findings are reviewed in detail in the Consultation dated 2 July, 2003 by Charles Lee, M.D., Medical Officer, Division of Pulmonary and Allergy Drug Products. The following is a brief overview of the studies and the findings.

Study 149-01-06: "Skin Testing for Allergic-Type Reactions to the Components of Abarelix Drug Product."

The Sponsor performed skin tests in 15 normal subjects and in 1 subject who had experienced pruritus and a raised, red rash on his chin from 3 to 48 hours after injections of abarelix on multiple occasions. The sponsor was not able to test any patients who had had an immediate onset systemic allergic reaction after dosing with abarelix in a clinical trial. In Study 149-01-06, skin tests were

positive to abarelix at concentrations of 0.001 mg/mL and 0.01 mg/mL in normal subjects. Skin tests were positive to abarelix at a concentration of 0.01 mg/mL in the one patient with a history of a delayed allergic reaction to abarelix. Skin tests were negative to sodium carboxymethylcellulose (NaCMC) at concentrations of 0.001 to 0.1 mg/mL in normal subjects and in the one patient with the history of a delayed allergic reaction.

Medical Officer's Comments

- *These results suggest that abarelix drug substance can cause non-specific mast cell degranulation, and that positive skin test results at abarelix concentrations of 0.001 mg/mL and higher are not related to IgE-mediated hypersensitivity. These data also suggest that the abarelix reactions could be due to an anaphylactoid or non-immune etiology. However, since no patients with immediate onset allergic reactions were tested, the possibility that these reactions were due to an immune etiology cannot be excluded. NaCMC did not appear to cause mast cell degranulation at any of the concentrations tested.*

Study PPI-02-02-401: "In Vitro Testing of IgE and IgG Levels in Retained Serum and Plasma Samples"

During the conduct of the controlled studies and some of the supportive clinical trials, plasma samples for detection of IgG antibodies to abarelix were collected at screening, at Days 85, 169, 253, and 337, and at the follow up visit. No IgG antibodies to abarelix were detected in these samples.

As part of their efforts to elucidate the mechanism(s) for the abarelix-induced allergic reactions, the Sponsor developed additional *in vitro* assays to detect the presence of (a) IgE antibodies to abarelix or carboxymethylcellose (CMC) and (b) IgG antibodies to CMC. Serum or plasma samples previously obtained during the conduct of the earlier clinical trials were assayed for immunoglobulins using these assay procedures.

Samples were assayed both from patients who had experienced allergic reactions and patients who had not experienced such reactions. For patients who had experienced an allergic reaction, samples collected prior to administration of the first dose and closest to the date of the allergic reaction were assayed. Samples were analyzed from 56 patients who had allergic reactions that included immediate onset hypotension/syncope, bronchoconstriction, angioedema, flushing, rash, urticaria, pruritus, dermatitis, and eczema. These 56 patients included 45 treated with abarelix, 10 treated with leuprolide, and one treated with goserelin. Samples included those from 5 patients who had immediate allergic reactions associated with hypotension or syncope after exposure to abarelix. Samples were also assayed from patients exposed to abarelix or leuprolide and who did not experience an allergic reaction. For these patients, the sample collected prior to administration of the first dose of Study Drug and the last available post-dose sample were assayed. These samples were from 30 abarelix-treated patients and 30 leuprolide treated patients.

The sponsor's *in vitro* testing results did not show any meaningful or consistent differences in abarelix-specific IgE, CMC-specific IgE or IgG, total IgE, or total IgG levels between abarelix-treated patients or Lupron- or Zoladex-treated patients or between patients who had allergic reactions and those who did not. Several patients were noted to have large changes in the values for one or more measurements; however, these changes were fairly evenly distributed across all groups of patients tested.

Medical Officer's Comments

- *These data suggest that the reactions observed in abarelix-treated patients during the clinical development program might not have an IgE or IgG-mediated etiology, and provide some evidence that the reactions might be anaphylactoid in nature.*

- *Based on the results from skin testing and the in vitro tests, the Sponsor concluded that the reactions noted in the abarelix development program were anaphylactoid, or non-immune in character. In support of this interpretation is the observation that one patient had an immediate onset allergic reaction following his first exposure to abarelix.*
- *The symptoms of an anaphylactoid reaction and anaphylaxis are similar because the chemical mediators of these reactions are similar or the same. The onset for both types of reaction is commonly within one hour after administration of the drug and frequently may be within minutes of dosing. Treatment for both is the same, and includes epinephrine, H1 and H2 antihistamines, intravenous fluids, corticosteroids, and bronchodilators if the event is associated with bronchospasm.*

7.16.2.5 Medical Officer's Overall Assessment of the Risk Associated with Immediate Onset Allergic Reactions in Patients Treated with Abarelix.

It is helpful to examine the frequency of anaphylaxis or anaphylactoid reactions for some approved drugs and pharmaceutical products to provide a frame of reference for abarelix (Table 82).

Table 82 Approximate Rates of Anaphylaxis/Anaphylactoid Events (Abarelix and Other Pharmaceutical Products)

Pharmaceutical Product	Anaphylaxis/Anaphylactoid Events (%of treatment courses)	Fatal Anaphylaxis (% of treatment courses)
Penicillin	0.01 to 0.05	0.001-0.002
Low osmolar RCM	0.04	NA
Hyperosmolar RCM	0.22	0.009
Abarelix	0.6 [1]	0 to date
ATG	2	NA
Paclitaxel	2 to 4	NA
Abacavir	5	NA
Aprotinin	<0.1 (initial exposure)	NA

[1] Based on Kaplan Meier analysis for events at 1 year of treatment.
Source: Consultation of 2 July, 2003 by Charles Lee, MD, Medical Officer, Division of Pulmonary and Allergy Drug Products, Regulatory Briefing of 28 May 2003, and Table 80 of this review.

The per injection frequency of anaphylaxis with abarelix of 0.04% (Sponsor's estimate) was similar to penicillin and low osmolar radiocontrast media, but lower than that for hyperosmolar radiocontrast media, ATG, and aprotinin. However, penicillin and radiocontrast media are generally not used chronically (i.e., once every 4 weeks) as would be the case for abarelix in the palliative treatment of advanced symptomatic prostate cancer. Because of the finding that the cumulative rate of reactions increased over time with the continued use of abarelix, the rate obtained from a life table (Kaplan Meier) analysis is a more appropriate representation of the risk. Based on such an analysis, the one-year event rate for a severe allergic reaction was estimated to be 0.61% (Table 80).

Although no patients have died or have been reported to have experienced any permanent sequelae from an abarelix-induced immediate systemic allergic reaction, such reactions represent a serious safety concern. The reported severity and incidence of these allergic reactions in the clinical trials, lead one to conclude that the risk-benefit ratio for abarelix would be acceptable only for the limited number of patients who would derive significant benefit from avoidance of a testosterone surge and the accompanying symptoms of a clinical flare. The indicated population should therefore be limited

to those patients with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: 1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.

Therefore as a prerequisite for approval, the Sponsor developed risk management procedures and education programs for medical care providers and patients to maximize the safe use of abarelix. The program will ensure that (1) only the indicated population is treated with abarelix and (2) physicians are qualified and capable of managing a severe allergic reaction (see Section 7.17, Risk Management Plan).

7.16.3 Hepatic Toxicity

Medical Officer's Comment

In Phase 1/2 Study 149-97-04, 4 patients were noted to have ALT increases of more than 3 x ULN. All resolved without sequelae, but because of this observation, liver function tests were monitored closely in all subsequent clinical trials. If a patient in the abarelix or Lupron treatment groups experienced an elevated ALT or AST value ≥ 5.1 x ULN (grade 3 toxicity, WHO toxicity scale), a repeat blood draw was to be performed 3, 7, and 12 days after the date of the abnormality. If there was not a significant improvement in laboratory values during this period, the patient was to be withdrawn. In the Lupron plus Casodex group, ALT or AST values > 2 x ULN were the reference levels used to determine if a patient should be withdrawn from treatment.

In this review, liver function test results and withdrawals due to liver-related adverse events for both the primary controlled safety studies (Studies 149-98-02, 149-98-03, 149-99-03) and the uncontrolled studies (Studies 149-97-04, Study 149-98-04, and Study 149-99-04) are presented. Laboratory tests of liver function in the clinical trials consisted of alkaline phosphatase, ALT (alanine transaminase; SGPT), AST (aspartate transaminase; SGOT), and total bilirubin. Laboratory results of liver function and liver damage are presented and discussed in the following order: (1) mean and median serum concentrations and mean and median changes from baseline at each protocol designated assessment time; (2) shifts from the normal range to values above the upper limit of the normal ranges, (3) clinically notable values. Findings are presented separately for each study and well as pooled for the 3 primary safety studies.

7.16.3.1 Liver Function Test Values (Changes from Baseline)

Mean and median values for liver function tests and absolute changes from baseline were reviewed for the primary safety studies. Changes across groups were similar for alkaline phosphatase, AST and total bilirubin. However, mean and median serum ALT values and mean absolute changes from baseline were higher in the abarelix group compared to those in the Lupron and Lupron plus Casodex groups (Table 83).

Medical Officer's Comments

- *The differences between mean values in the abarelix group and Lupron group were relatively small (< 5 IU/L) and most apparent after Study Day 169.*

Table 83. Mean Serum ALT (IU/L) and Absolute Changes from Baseline during Treatment (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

Statistic	Serum ALT (IU/L)		
	Lupron (N = 284)	Lupron +Casodex (N= 83)	Abarelix (N = 735)
Baseline			
Mean	23.1	20.9	23.3
Min, Max			
N	284	93	735
Day 15			
Mean	24.6	20.9	28.7
Min. Max			
Mean change	**1.5**	**0.2**	**5.3**
Day 29			
Mean	31.0	22.7	33.2
Min. Max			
Mean change	**8.0**	**1.7**	**9.9**
Day 85			
Mean	29.6	22.9	28.5
Min. Max			
Mean change	**6.5**	**2.1**	**5.3**
Day 169			
Mean	24.0	21.5	26.8
Min. Max			
N	250	69	660
Mean change	**1.2**	**1.4**	**4.1**
Day 253			
Mean	21.9	22.2	26.2
Min. Max			
N	52	40	209
Mean change	**0.2**	**3.3**	**4.7**
Day 365			
Mean	22.9	22.0	24.1
Min. Max			
N	44	32	180
Mean change	**0.6**	**3.3**	**2.4**

Source: Table 5.4.1.1, pg 55, Supplemental Safety Submission, March 27, 2001.

7.16.3.2 Shift in Liver Function Test Values to High (>ULN)

Shifts in liver function test values to above the upper limit of the normal range are listed by study for the controlled studies (Table 84) and the uncontrolled studies (Table 86). Pooled results for the controlled studies are presented in Table 85. In the controlled studies, the percentage of subjects exhibiting shifts from normal to high, low to high, or unknown to high was similar (no more than ±4% difference) across the abarelix and Lupron groups for alkaline phosphatase, AST, and bilirubin in Studies 149-98-02 and 149-99-03. The differences in the mean percentages of patients shifting to high for ALT, however, were consistently greater in the abarelix group in the controlled studies and ranged from 7% in Study 149-99-03 to 20% in Study 149-98-03. The mean percentages of subjects with increased AST values was higher in the abarelix group compared to the Lupron plus Casodex group but not higher relative to the Lupron groups.

Table 85 includes pooled data from the controlled studies. The comparisons presented in Table 85 include data from patients treated only with Lupron plus Casodex (Study 149-98-03) as well as data pooled across studies from (1) patients treated with Lupron alone (Studies 149-98-02 and 149-99-03), (2) patients treated with Lupron alone or Lupron plus Casodex (Studies 149-98-02, 149-98-03, and 149-99-03), and (3) all patients treated with abarelix in the controlled studies (Studies 149-98-02, 149-98-03, and 149-99-03). Data in Table 85 are also presented in terms of 3 treatment intervals (Days 1-169, Days 1-365, and Days after 169. The percentages of patients with shifts to high (> ULN) for ALT in the abarelix group are greater than in any of the Lupron groups in each of the 3 assessment intervals. *Of clinical importance is the observation that the percentages of patients with shifts to high (> ULN) for bilirubin in the combined abarelix group are comparable to those in the Lupron groups.*

In the uncontrolled studies (Table 86), the percentages of patients treated with abarelix with shifts in liver function test values from not high to high were similar to those observed in the controlled studies.

The Sponsor also performed additional shift analyses that considered not only whether a patient's laboratory value increased to above the ULN but the magnitude of the increase as well, based on WHO toxicity grades. These analyses are presented for ALT in Table 87 (all 3 controlled studies for the interval Days 1-169 and Days 1-365 presented separately) and for AST in Table 88. In the pooled analysis for the 3 controlled safety studies, 156 (21%), 26 (4%) and 1 (<1%) of the abarelix-treated patients with Grade 0 toxicity at baseline, had one or more ALT values with Grade 1, Grade 2, or Grade 3 toxicity, respectively, during Study Days 1-169 (Table 87, upper panel). Changes of similar magnitude were observed for ALT values in the abarelix group for the period Days 1-365.

Medical Officer's Comments

- *The shift analysis for liver function tests from the 3 controlled studies are consistent across the studies in that each demonstrated that a higher percentage of abarelix-treated patients, compared to Lupron-treated patients, had shifts in ALT values from not elevated to elevated (> ULN).*
- *The shift analyses that also took into account the magnitude of the changes in ALT values, based on WHO toxicity grades, indicated that the magnitude of the shift in the abarelix group was generally 1 toxicity grade, and less frequently, 2 or more grades.*
- *The lower percentages of patients that shifted from not high to high in the Lupron plus Casodex compared to either the abarelix group or the Lupron group is a surprising observation in that hepatotoxicity is a known complication of treatment with antiandrogens.*
- *Perhaps of most significance to the safety assessment of abarelix in terms of hepatotoxicity, is the observation that the percentages of patients with shifts to high for bilirubin in the abarelix groups are comparable to those in the Lupron groups in the controlled studies (Table 84).*

Table 84. Liver Function Test Shifts to High (>ULN) in Controlled Studies

Study 149-98-02				
	Lupron Depot (N = 89)		Abarelix Depot (N = 180)	
Laboratory Test	Evaluable (n) [1]	Experienced (n,%) [2]	Evaluable (n)	Experienced (n,%)
Alkaline phosphatase	85	13 (15)	171	23 (13)
ALT	82	29 (35)	171	77 (45)
AST	82	29 (35)	172	61 (35)
Total bilirubin	88	1 (1)	176	0
Study 149-98-03				
	Lupron Depot + Casodex (N = 83)		Abarelix Depot (N = 168)	
Laboratory Test	Evaluable (n)	Experienced (n,%)	Evaluable (n)	Experienced (n,%)
Alkaline phosphatase	79	10 (13)	158	21 (13)
ALT	80	19 (24)	159	70 (44)
AST	81	13 (16)	163	53 (33)
Total bilirubin	75	0	166	4 (2)
Study 149-99-03				
	Lupron Depot (N = 195)		Abarelix Depot (N = 387)	
Laboratory Test	Evaluable (n)	Experienced (n,%)	Evaluable (n)	Experienced (n,%)
Alkaline phosphatase	187	20 (11)	363	54 (15)
ALT	182	63 (35)	356	150 (42)
AST	191	58 (30)	366	117 (32)
Total bilirubin	191	9 (5)	380	7 (2)

[1] Patients whose baseline value was not high and who had a least 1 post-baseline value.
[2] Shifts to high include normal to high, low to high, and unknown to high. Values represent the number and proportion (%) of patients experiencing the shift to high.
Source: Table 10-14, Vol. 1.52; Table 10.5.2.2, Vol. 67; and Table 9-17, Vol. 1.77 (Submission of December 2000).

Table 85. Liver Function Test Shifts to High (>ULN) in Controlled Studies (Studies 149-98-02, 149-98-03, 149-99-03, Combined Analysis).

	Lupron [A] N = 284		(Lupron+Casodex)[B] N = 83		Lupron plus (Lupron+Casodex)[C] N = 367		Abarelix Depot [C] N = 735	
Laboratory Test	Eval[1] N	Shifted [2] N (%)	Eval N	Shifted N (%)	Eval N	Shifted N (%)	Eval N	Shifted N (%)
Alkaline Phos.								
Days 1-169 [3]	272	30 (11)	79	7 (9)	351	37 (11)	692	87 (13)
Days 1-365 [4]	85	13 (15)	79	10 (13)	164	23 (14)	329	44 (13)
After Day 169 [4]	71	7 (10)	63	4 (6)	134	11 (8)	295	28 (9)
ALT								
Days 1-169	264	89 (34)	80	14 (18)	344	103 (30)	686	278 (41)
Days 1-365	82	29 (35)	80	19 (24)	162	48 (30)	330	147 (45)
After Day 169	68	10 (15)	65	10 (15)	133	20 (15)	296	55 (19)
AST								
Days 1-169	275	82 (30)	81	11 (14)	356	93 (26)	701	213 (30)
Days 1-365	84	29 (35)	81	13 (16)	165	42 (25)	335	114 (34)
After Day 169	69	11 (16)	65	4 (6)	134	15 (11)	301	42 (14)
Bilirubin								
Days 1-169	279	10 (4)	75	0	354	10 (3)	722	10 (1)
Days 1-365	88	1 (1)	75	0	163	1 (1)	342	4 (1)
After Day 169	73	0	59	0	132	0	305	1 (<1)

[A] Data pooled across Studies 149-98-02 and 149-99-03.
[B] Study 149-98-03 only.
[C] Data pooled across Studies 149-98-02, 149-98-03, and 149-99-03.
[1] Patients whose baseline value was not high and who had a least 1 lab result in the specified period.
[2] Shifts to high include normal to high, low to high, and unknown to high. Values represent the number and proportion (%) of patients experiencing the shift to high.
[3] Includes Studies 149-98-02, 149-98-03, and 149-99-03.
[4] Includes only Studies 149-98-02 and 149-98-03.
Source: Table 5.4.2.1, supplemental safety submission, March 27, 2001.

Table 86. Liver Function Test Shifts to High (>ULN) in Uncontrolled Studies

Study 149-97-4				
	Abarelix Depot Phase 1 (N = 54) [1]		Abarelix Depot Phase II (N = 209) [2]	
Laboratory Test	Evaluable (n) [3]	Experienced (n) [4]	Evaluable (n)	Experienced (n,%)
Alkaline phosphatase	52	6	198	30 (15)
ALT	48	16	197	74 (38)
AST	50	15	202	54 (27)
Total bilirubin	53	1	201	4 (2)
Study 149-98-04				
			Abarelix Depot 100 mg (N = 81)	
Laboratory Test			Evaluable (n)	Experienced (n,%)
Alkaline phosphatase			41	8 (20)
ALT			75	25 (33)
AST			74	21 (28)
Total bilirubin			79	1 (1)
Study 149-99-4				
	Abarelix Depot 50 mg (N = 14)		Abarelix Depot 100 mg (N = 278)	
Laboratory Test	Evaluable (n) [5]	Experienced (n,%)	Evaluable (n)	Experienced (n,%)
Alkaline phosphatase	12	5 (42)	258	38 (15)
ALT	12	3 (25)	255	54 (21)
AST	13	5 (38)	261	48 (18)
Total bilirubin [6]	13	2 (15)	273	4 (1)

[1] Patients received induction abarelix doses ranging from 20-150 mg.
[2] Patients received monthly maintenance abarelix doses of 50 mg or 100 mg.
[3] Shifts to high include normal to high, low to high, and unknown to high.
[4] Patients whose baseline value was not high and who had a least 1 post-baseline value.
[5] Patients whose baseline value on Study 149-99-04 was not high and who had a least 1 post-baseline value.
[6] In each case, total bilirubin ≤ 1.5 mg/dL and without concurrent transaminase elevations.

Source: Table 10-15, pg 107 of Study Report for 149-97-04 (Vol. 1.91); Table 10-12, pg 170 of Study Report for 149-98-04 (Vol. 42.19); and Table 10-12, pg 54 of Study Report for 149-99-04 (Vol. 42.27). (Submissions of December 2000 and February 2003).

Table 87. ALT Shift in Toxicity Grade - Baseline to Most Extreme On-Study Value through Day 169 (Top) or Day 365 (Lower) Table (Pooled Data from Controlled Studies 149-98-02, 149-98-03, and 149-99-04)

		Baseline																	
		Lupron Depot [n, (%)]						Lupron Depot + Casodex [n, (%)]						Abarelix Depot [n, (%)]					
	Grade[1]	0	1	2	3	4	Total	0	1	2	3	4	Total	0	1	2	3	4	Total
Highest On Study Grade (Days 1 to 169)	N/A	1 (<1)	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
	0	215 (76)	0	0	0	0	215	75 (90)	0	0	0	0	75	518 (71)	5 (1)	0	0	0	523
	1	46 (16)	4 (1)	0	0	0	50	6 (7)	0	0	0	0	6	156 (21)	12 (2)	1 (<1)	0	0	169
	2	11 (4)	4 (1)	0	0	0	15	1 (1)	0	0	0	0	1	26 (4)	4 (1)	0	0	0	30
	3	2 (<1)	0	0	0	0	2	1 (1)	0	0	0	0	1	10 (1)	1 (<1)	0	0	0	11
	4	0	1 (<1)	0	0	0	1	0	0	0	0	0	0	1 (<1)	0	0	0	0	1
	Total	275	9	0	0	0	284	83	0	0	0	0	83	712	22	1	0	0	735

		Baseline																	
		Lupron Depot [n, (%)]						Lupron Depot + Casodex [n, (%)]						Abarelix Depot [n, (%)]					
	Grade	0	1	2	3	4	Total	0	1	2	3	4	Total	0	1	2	3	4	Total
Highest On Study Grade Days 1 to 365)	N/A	1 (<1)	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
	0	213 (75)	0	0	0	0	213	72 (87)	0	0	0	0	72	500 (68)	5 (1)	0	0	0	505
	1	48 (17)	4 (1)	0	0	0	52	9 (11)	0	0	0	0	9	172 (23)	11 (<2)	1 (<1)	0	0	184
	2	11 (4)	4 (1)	0	0	0	15	1 (1)	0	0	0	0	1	28 (4)	5 (1)	0	0	0	33
	3	2 (<1)	0	0	0	0	2	1 (1)	0	0	0	0	1	10 (1)	1 (<1)	0	0	0	11
	4	0	1 (<1)	0	0	0	1	0	0	0	0	0	0	1 (<1)	0	0	0	0	1
	Total	275	9	0	0	0	284	83	0	0	0	0	83	712	22	1	0	0	735

[1] Toxicity Grade: 0 = ≤1.25 x ULN; 1 = 1.26 -< 2.6 x ULN; 2 = 2.6 - < 5.1 x ULN; 3 = 5.1 – 10 x ULN; 4 = > 10 x ULN.
Numbers in each square represent the actual number of patients in the category and the percentage of patients (enclosed in brackets) relative to the total treatment group.
Source: Table 5.4.3, pg 111, ISS Vol. 1.110; Table 5.4.3.A of Chemistry Supplement of 27 March 2001. Percentages calculated by medical reviewer.

Table 88. AST Shift in Toxicity Grade - Baseline to Most Extreme On-Study Value through Day 169 (Top) or Day 365 (Lower) Table (Pooled Data from Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

		Baseline																	
		Lupron Depot [n, (%)]						Lupron Depot + Casodex [n, (%)]						Abarelix Depot [n, (%)]					
	Grade[1]	0	1	2	3	4	Total	0	1	2	3	4	Total	0	1	2	3	4	Total
Highest On Study Grade (Days 1 to 169)	N/A	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
	0	243 (86)	1 (<1)	0	0	0	244	78 (94)	0	0	0	0	78	607 (83)	2 (<1)	0	0	0	609
	1	31 (11)	1 (<1)	0	0	0	32	3 (4)	1 (1)	0	0	0	4	106 (14)	3 (<1)	0	0	0	109
	2	3 (1)	2 (1)	0	0	0	5	1 (1)	0	0	0	0	1	10 (1)	1 (<1)	0	0	0	11
	3	0	1 (<1)	0	0	0	1	0	0	0	0	0	0	3 (<1)	0	0	0	0	3
	4	1 (<1)	0	0	0	0	1	0	0	0	0	0	0	2 (<1)	0	0	0	0	2
	Total	279	5	0	0	0	284	82	1	0	0	0	83	729	6	0	0	0	735

		Baseline																	
		Lupron Depot [n, (%)]						Lupron Depot + Casodex [n, (%)]						Abarelix Depot [n, (%)]					
	Grade	0	1	2	3	4	Total	0	1	2	3	4	Total	0	1	2	3	4	Total
Highest On Study Grade Days 1 to 365)	N/A	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	1
	0	242 (86)	0	0	0	0	242	78 (94)	0	0	0	0	0	597 (81)	2 (<1)	0	0	0	599
	1	31 (11)	2 (1)	0	0	0	33	3 (4)	1 (1)	0	0	0	0	114 (16)	3 (<1)	0	0	0	117
	2	4 (1)	2 (1)	0	0	0	6	1 (1)	0	0	0	0	0	11 (1)	1 (<1)	0	0	0	12
	3	0	1 (<1)	0	0	0	1	0	0	0	0	0	0	4 (<1)	0	0	0	0	4
	4	1 (<1)	0	0	0	0	1	0	0	0	0	0	0	2 (<1)	0	0	0	0	2
	Total	279	5	0	0	0	284	82	1	0	0	0	83	729	6	0	0	0	735

[1] Toxicity Grade: 0 = ≤1.25 x ULN; 1 = 1.26 -< 2.6 x ULN; 2 = 2.6 - < 5.1 x ULN; 3 = 5.1 – 10 x ULN; 4 = > 10 x ULN
Numbers in each square represent the actual number of patients in the category and the percentage of patients (enclosed in brackets) relative to the total treatment group.
Source: Table 5.4.3, pg 112, ISS, Vol. 1.110; Table 5.4.3A, pg 415 of Chemistry Supplement of 27 March 2001. Percentages calculated by medical reviewer.

7.16.3.3 Clinically Notable Liver Function Test Values

Clinically notable liver function test values are listed by study for the primary controlled studies (Table 89) and the primary uncontrolled studies (Table 91). Pooled results for the controlled studies are presented in Table 90. The percentages of patients exhibiting clinically notable laboratory values for liver function tests in the abarelix and Lupron groups were generally similar in Study 149-98-02, but slightly higher in the abarelix group for the categories of alkaline phosphatase (>5.0 x ULN) and ALT (>200 U/L) in Study 149-99-03. In Study 149-98-03, the percentages of patients exhibiting clinically notable laboratory values were higher in the abarelix group compared to the Lupron plus Casodex group for all categories except bilirubin (Table 89).

Data for the controlled studies also were pooled across studies in a manner similar to that described previously in Section 7.16.3.2. In the combined comparisons for the controlled studies (Table 90), there was a numerically higher (albeit small) percentage of patients in the abarelix group, compared to the Lupron alone and Lupron plus Casodex groups, who exhibited clinically notable values for ALT and alkaline phosphatase.

The percentages of abarelix treated patients with clinically notable values in the uncontrolled studies were similar to those in the controlled studies with one exception. There was a markedly higher percentage of patients in the abarelix group (20-42%) that had notable alkaline phosphatase values in Study 149-98-04.

Medical Officer's Comments

- *Although the percentages of patients with clinically notable laboratory values in the pooled comparisons were higher for alkaline phosphatase, ALT and AST in the abarelix group compared to the combined Lupron and Lupron plus Casodex groups, the differences were small. The differences for clinically notable values ranged from 0.1% for AST values > 2.5 x ULN to 1.6% for ALT values > 2.5 x ULN, all higher in the abarelix-treated patients.*
- *The lower percentages of subjects with clinically notable values in the Lupron plus Casodex group, compared to either the Lupron or the Lupron plus Casodex group is surprising since Casodex, per se, has been reported to produce some degree of liver toxicity.*
- *Only 1 patient in each of the abarelix and Lupron groups had a bilirubin levels > 2.5 x ULN. Neither elevation was attributed to treatment with Study Drugs but rather to a concomitant illness (i.e., pancreatic cancer in the abarelix-treated patient and cholecystitis and pancreatitis in the Lupron-treated patient).*
- *The high proportion of patients with clinically notable alkaline phosphatase values in Study 149-98-04 is most likely a consequence of a higher proportion of patients with advanced prostate cancer and the higher incidence of bone metastases in the such a population.*

Table 89. Clinically Notable Liver Function Test Results in Controlled Studies

Study 149-98-02

Laboratory Test	Cutoff Value	Lupron (N = 89) Evaluable[1] n	Lupron (N = 89) Experienced[2] n (%)	Abarelix (N = 180) Evaluable[1] n	Abarelix (N = 180) Experienced n (%)
Alkaline phosphatase	> 200 U/L	89	3 (3.4)	180	5[3] (2.8)
	> 5.0 x ULN	89	1 (1.1)	180	0
ALT	> 2.5 x ULN	89	5 (5.6)	180	11 (6.1)
	> 200 U/L	89	1 (1.1)	180	1 (0.6)
AST	> 2.5 x ULN	89	4 (4.5)	180	4 (2.2)
	> 200 U/L	89	0	180	0
Total bilirubin	> 2.5 x ULN	89	0	180	0

[1] Patients whose baseline value was not in the clinically notable range or whose post-baseline value was worse than their clinically notable baseline value.
[2] Number and percent of patients who developed a clinically notable value in the respective category.
[3] Determined to be of bone origin.
Source: Table 10-15, pg 68, Vol. 1.52, Submission of December 2000.

Study 149-98-03

Laboratory Test	Cutoff Value	Lupron + Casodex (N = 83) Evaluable[1] n	Lupron + Casodex (N = 83) Experienced n (%)	Abarelix (N = 168) Evaluable[1] n	Abarelix (N = 168) Experienced n (%)
Alkaline phosphatase	> 5.0 x ULN	83	0	166	1 (0.6) [2]
	> 200 U/L	83	0	166	7 (4.2)
ALT	> 2.5 x ULN	83	2 (2.4)	167	15 (9.0)[2, 3]
	> 200 U/L	83	1 (1.2)	167	4 (2.4) [2]
AST	> 2.5 x ULN	83	2 (2.4)	168	9 (5.4)[2, 3]
	> 200 U/L	83	0	168	3 (1.8) [2]
Total bilirubin	> 2.5 x ULN	83	0	168	0

[1] Patients whose baseline value did not exceed the cutoff value and who had at least 1 post-baseline value.
[2] Elevations in Patient 38-3135 attributed to pancreatic carcinoma.
[3] Elevations in Patient 38-3126 attributed to Dilantin® toxicity.
Source: Table 10-15, pg 72, Vol. 1.76, Submission of December 2000.

Study 149-99-03

Laboratory Test	Cutoff Value	Lupron (N =195) Evaluable[1] n	Lupron (N =195) Experienced n (%)	Abarelix (N =387) Evaluable[1] n	Abarelix (N =387) Experienced n (%)
Alkaline phosphatase	> 200 U/L	194	6 (3.1)[2,3]	386	15 (3.9)[4,5,6]
	> 5.0 x ULN	194	1 (0.5)	386	6 (1.6)[4,6]
ALT	> 2.5 x ULN	194	17 (8.8)[2,3]	386	34 (8.8)[4,5]
	> 200 U/L	194	2 (1.0)[2,3]	386	8 (2.1)[4,5]
AST	> 2.5 x ULN	194	5 (2.6)[2,3]	386	10 (2.6)[4,5]
	> 200 U/L	194	2 (1.0)[2,3]	386	3 (0.8)[5]
Total bilirubin	> 2.5 x ULN	194	1 (0.5)[2]	386	1 (0.3)[4]

[1] Patients whose baseline value did not exceed the cutoff value and had at least 1 post-baseline value.
[2] Elevations in patient 320-2371 attributed to cholecystitis, pancreatitis, and obstructive jaundice.
[3] Elevations in patient 316-1055 attributed to hepatitis C.
[4] Elevations in patient 317-1216 attributed to pancreatic cancer.
[5] Elevations in patient 308-1117 attributed to history of liver function tests elevations.
[6] Elevations in patient 330-3443 attributed to liver metastases.
Source: Table 9.18, pg 90, Vol. 1.77, Submission of December 2000.

Table 90. Clinically Notable Liver Function Test Values (Pooled Studies 149-98-02, 149-98-03, 149-99-03)

	Treatment Group											
	Lupron [A] (N=284)			Lupron + Casodex[B] (N=83)			Lupron + (Lupron + Casodex)[C] (N=367)			Abarelix [C] (N=735)		
Laboratory Test	Eval[1] n	Experienced[2] n	(%)	Eval n	Experienced n	(%)	Eval n	Experienced n	(%)	Eval n	Experienced n	(%)
Alkaline Phos.												
> 200 U/L	283	9	(3.2)	83	0		366	9	(2.5)	732	21	(2.8)
> 5.0 x ULN	283	2	(0.7)	83	0		366	2	(0.5)	732	13	(1.8)
ALT												
> 2.5 x ULN	283	22	(7.8)	83	2	(2.4)	366	24	(6.6)	733	60	(8.2)
> 200 U/L	283	3	(1.1)	83	1	(1.2)	366	4	(1.1)	733	13	(1.8)
AST												
> 2.5 x ULN	283	9	(3.2)	83	2	(2.4)	366	11	(3.0)	734	23	(3.1)
> 200 U/L	283	2	(0.7)	83	0		366	2	(0.5)	734	6	(0.8)
Total bilirubin												
> 2.5 x ULN	283	1	(0.4)	83	0		366	1	(0.3)	734	1	(0.1)

[A] Data pooled across Studies 149-98-02 and 149-99-03.
[B] Study 149-98-03 only.
[C] Data pooled across Studies 149-98-02, 149-98-03, and 149-99-03
[1] Number of patients in respective category for whom one or more on treatment values were available.
[2] Number and percent of patients who developed a clinically notable value in the respective category.
Source: Table 89 of this review (Calculated by medical reviewer).

Table 91. Clinically Notable Liver Function Test Results in Uncontrolled Studies

Study 149-97-4

Laboratory Test	Cutoff Value	Abarelix Phase I (N = 54) Evaluable[1] n	Abarelix Phase I (N = 54) Experienced[2] n (%)	Abarelix Phase II (N = 209) Evaluable n	Abarelix Phase II (N = 209) Experienced n (%)
Alkaline phosphatase	> 200 U/L	53	3	209	11 (5)
	> 5.0 x ULN	53	1	209	1 (<1)
ALT	> 2.5 x ULN	54	4	209	6 (3)
	> 200 U/L	54	1	209	1(<1)
AST	> 2.5 x ULN	54	1	209	6 (3)
	> 200 U/L	54	1	209	0
Total bilirubin	> 2.5 x ULN	54	0	290	0

[1] Included patients whose screening value was not in the clinically notable range and patients whose post screening value was worse than their clinically notable screening value.
[2] Number and percent of patients who developed a clinically notable value in the respective category.
Source: Table 12.7.8, pg 369, Vol. 1.92 of 149-47-03 Study Report, submission of December 2000.

Study 149-98-04

Laboratory Test	Cutoff Value	Abarelix Depot (N = 81) Evaluable n	Abarelix Depot (N = 81) Experienced n (%)
Alkaline phosphatase	> 5.0 x ULN	79	33 (42)
	> 200 U/L	79	16 (20)
ALT	> 2.5 x ULN	80	2 (3)
	> 200 U/L	80	1 (1)
AST	> 2.5 x ULN	78	3 (4)
	> 200 U/L	78	0
Total bilirubin	> 2.5 x ULN	80	0

Source: Table 10-13, pg 171, Vol. 42.19 of 149-98-04 Study Report, submission of February 2003.

Study 149-99-04

Laboratory Test	Cutoff Value	Abarelix Depot 50 mg (N =14) Evaluable[1] n	Abarelix Depot 50 mg (N =14) Experienced n (%)	Abarelix Depot 100 mg (N = 278) Evaluable n	Abarelix Depot 100 mg (N = 278) Experienced n (%)
Alkaline phosphatase	> 200 U/L	14	0	275	8 (3)
	> 5.0 x ULN	14		275	2 (1)
ALT	> 2.5 x ULN	14	1 (7)	274	7 (3)
	> 200 U/L	14		275	2 (1)
AST	> 2.5 x ULN	14	0	275	8 (3)
	> 200 U/L	14		275	2 (1)
Total bilirubin	> 2.5 x ULN	14	0	275	1 (<1)[2]

[1] Patients whose baseline value on Study 149-99-04 was not in the clinically notable range or whose post-baseline value was worse than their clinically notable baseline value.
[2] Elevations in patient 441-4042 attributed to poorly differentiated metastatic GI adenocarcinoma.
Source: Table 10-13, pg 55, Vol. 42.27 of 149-99-04 Study Report.

7.16.3.4 Patient Withdrawals due to Increased Transaminase Levels

In compliance with the protocol, Study Drug was to be discontinued if any transaminase elevation > 5.1 x ULN in a patient treated with Lupron alone or abarelix continued to be elevated to > 3 x ULN within 12 days of the initially observed elevation. Patients treated with Lupron plus Casodex were to be withdrawn from treatment if a transaminase elevation > 2 x ULN continued to be elevated to > 2 x ULN within 7 days of the initial observed elevation.

Primary Controlled Safety Studies. In the primary controlled clinical trials, 4 patients in the abarelix group and 2 patients in the Lupron plus Casodex group developed transaminase elevations that required withdrawal in accordance with the study protocols (Table 92). No patients receiving Lupron alone were withdrawn because of elevated transaminase levels. An additional 3 patients receiving abarelix were withdrawn without having met the criteria for mandatory withdrawal per the study protocol. All elevations were assessed as possibly, probably, or definitely related to treatment with Study Drugs with one exception. The elevated transaminase levels in Patient No. 308-1117 were not thought to be related to treatment with abarelix, based on the patient's prior history of liver enzyme abnormalities.

Table 92 Patient Withdrawals Because of Elevated Transaminase Levels (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)

Study	Patient	Required Withdrawal[1]	Peak Value ALT (IU/mL)	Peak Value AST (IU/mL)	Peak Value Bilirubin (mg/dL)[5]	Relation to Study Drug
Lupron (N = 284)						
	None					
Lupron plus Casodex (N = 83)						
149-98-03	27-3049	Yes	> 4 x ULN	> 2 x ULN	.6	Definite
" "	03-3144	Yes	> 7 x ULN	> 3 x ULN	.5	Possible
Abarelix (N = 735)						
149-98-02	37-2160	Yes	> 9 x ULN	5 x ULN	.6	Definite
149-98-03	09-3036	Yes	> 6 x ULN	> 3 x ULN	1.1	Definite
" "	50-3085[2]	No[3]	> 4 x ULN	>7 x ULN	.8	Probably
149-99-03	308-1117	Yes	> 7 x ULN	> 4 x ULN	2.8[6]	Not Related
" "	338-1259	Yes	8 x ULN	> 4 x ULN	.6	Possibly
" "	332-1562	No[4]	2.7 x ULN	1.8 x ULN	.6	Possibly
" "	357-2331	No[4]	> 3 x ULN	1 x ULN	.5	Possibly

[1] Withdrawal required by protocol based on magnitude of transaminase elevation.
[2] Patient had a posttreatment liver biopsy that was interpreted as compatible with a "chemical hepatitis" probably due to treatment with abarelix. Patient, however, had been switched to treatment with goserelin prior to obtaining the biopsy thus making relationship to treatment with abarelix somewhat less clear.
[3] Patient elected to withdraw from study before mandatory criteria were met.
[4] Investigator's decision to withdraw patient.
[5] Upper limit of normal = 1.2 mg/dL.
[6] Single elevated value.

Medical Officer's Comments

- *None of the 284 patients (0%) who were treated with Lupron alone and 2 of the 83 patients (2.4%) treated with Lupron plus Casodex were terminated because of elevated transaminase levels. Seven (7) of the 735 patients (0.95%) treated with abarelix were terminated because of elevated transaminase levels. If one considers only those patients whose withdrawal was required by the protocol-defined criteria, 2 of 367 patients(0.54%) in the active control group*

and 4 of 735 patients(0.54%)in the abarelix group were withdrawn because of elevated serum transaminase levels.

- *Although 7 of 735 patients treated with abarelix in the controlled studies were withdrawn because of elevated transaminase levels, only one of these patients (No. 308-1117 in whom the elevation was not attributed to treatment with abarelix based on the patient's prior history of liver enzyme abnormalities) had a single elevated bilirubin value (see Table 92).*
- *Although abarelix appears to have greater hepatotoxicity than Lupron alone, no patient under the conditions of these controlled clinical trials experienced serious or irreversible liver damage as assessed by serum bilirubin levels. However, it should be noted that transaminase levels in the controlled clinical trials were monitored monthly or more frequently.*
- *The adverse effects of abarelix on the liver appear to be a manageable risk that will be addressed in labeling and will require period monitoring of serum transaminase levels.*

7.16.3.5 Medical Officer's Overall Assessment of Risk Related to Hepatic Toxicity in Abarelix-Treated Patients

In the primary controlled clinical trials, abarelix exhibited somewhat greater hepatic toxicity than Lupron alone or Lupron plus Casodex based on (1) the percentages of patients with a shift in normal transaminases levels at baseline to values > ULN at the end of treatment, (2) the percentages of patients with clinically notable on-treatment transaminase values; and the percentages of patients who were withdrawn from treatment because of elevated transaminase values. Of the 7 abarelix-treated patients who were withdrawn from the controlled studies, only one of these patients (No. 308-1117 in whom the elevation was not attributed to treatment with abarelix based on the patient's prior history of liver enzyme abnormalities) had a single elevated bilirubin value. No abarelix-treated patient under the conditions of these controlled clinical trials or in Trial 149-98-04 (the indicated population) experienced serious liver damage as assessed by serum bilirubin levels. The adverse effects of abarelix on the liver appear to be a manageable risk that will be addressed in labeling and will require period monitoring of serum transaminase levels during treatment.

7.16.4 Changes in QT Interval

The possible effect of abarelix treatment on the QT interval was not initially assessed in any of the clinical trials conducted in North America. ABACAS 1, conducted entirely in Europe, was the first clinical trial in which the possible effect of treatment with abarelix and a GnRH agonist on the QT interval was investigated in the abarelix development program. ABACAS 1 was a randomized clinical trial in which men with prostate were assigned to active treatment for up to 1 year with either abarelix (n = 87) or Zoladex plus Casodex (n = 90). A standard 12-lead ECG was performed during screening and on Study Days 84 and 336. Some patients had additional unscheduled ECGs. According to the Sponsor, an independent cardiologist initially interpreted the tracings on a blinded basis.

Results revealed that both treatments were associated with prolongation of the QT interval, the Sponsor asked an academic consultant to provide an independent blinded analysis of the QT changes observed in Study ABACAS 1. The Sponsor also contacted the Investigators of Studies 149-98-02 and 149-98-03 and requested a copy of all ECGs so that information about the QT interval could be obtained. Although ECGs were obtained at screening and at Study Day 169, the ECG information collected on the case report forms (CRFs) for these studies included only an overall interpretation of the ECG and a comment if there was a clinically significant abnormality. The CRFs did not specifically request information about the QT interval.

7.16.4.1 Sponsor's Analyses of QTc Interval Changes

The results of the Sponsor's per protocol analyses of the ABACAS 1 ECG data and the post hoc analyses of the ECG data from Studies 149-98-02 and 149-98-03 are summarized in Table 93 and Table 94. There was a numeric increase in the mean of the on-treatment QTc interval, relative to baseline, in each of the treatment groups in the 3 clinical trials (Table 93). The mean increase in the abarelix treatment groups was about 12.0 msec. In ABACAS 1, the mean increase was numerically greater in the Zoladex plus Casodex group (18.3 msec) compared to that in the abarelix group (i.e., 12.0 msec). In the combined data from Studies 149-98-02 and 149-98-03, the mean increase in the Lupron group (17.8 msec) was numerically greater than that in either the abarelix group (12.5 msec) or the Lupron plus Casodex group (9.8 msec).

Table 93 Sponsor's Analyses of QTc Interval Changes (Studies ABACAS 1, 149-98-02, and 149-98-03)

Parameter	Mean QTc Values (msec) [1]				
	ABACAS 1		149-98-02 and 149-98-03		
	Abarelix N = 82	Zoladex + Casodex N = 86	Abarelix N = 188	Lupron N = 46	Lupron + Casodex N = 34
Baseline	407.6	404.0	411.9	414.9	414.4
Post baseline [2]	419.5	422.4 [3]	424.1	432.7	424.1
Change from baseline	12.0	18.3 [3]	12.5	17.8	9.8

[1] Values corrected by Fridericia formula.
[2] Mean of all post baseline values.
[3] N = 84.
Source: Submission of July 9, 2003, pg 16 and 18.

The Sponsor's analyses of the QTc interval outliers are presented in Table 94. In ABACAS 1, the percentages of patients with a QTc increase from baseline of ≥ 60 msec or with a maximum on-treatment values of ≥ 500 msec was numerically slightly greater in the Zoladex plus Casodex treatment group. In Studies 149-98-02 and 149-98-03, the percentages of abarelix-treated patients with a QTc increase from baseline of ≥ 60 msec or with a maximum on-treatment values of ≥ 500 msec was numerically comparable to (Lupron alone) or numerically somewhat greater (Lupron plus Casodex) than that in the active comparator groups.

Table 94 Sponsor's Analyses of QTc Outliers (Studies ABACAS 1, 149-98-02, and 149-98-03)

QTc value (actual or increase from baseline) [1]	Number (%) of Patients				
	ABACAS 1		149-98-02 and 149-98-03		
	Abarelix N = 82	Zoladex + Casodex N = 84	Abarelix N = 188	Lupron N = 46	Lupron + Casodex N = 34
Maximum change from baseline					
≤ 30 msec	48 (59%)	38 (45%)	145 (77%)	30 (65%)	25 (74%)
> 30 msec to < 60 msec	32 (39%)	39 (46%)	34 (18%)	14 (30%)	9 (26%)
≥ 60 msec	2 (2%)	7 (8%)	9 (5%)	2 (4%)	0 (0%)
Maximum on-treatment value					
≤ 430 msec	34 (41%)	34 (40%)	91 (48%)	14 (30%)	16 (47%)
> 430 to ≤ 450 msec	22 (27%)	25 (30%)	47 (25%)	13 (28%)	14 (41%)
> 450 to ≤ 470 msec	18 (22%)	11 (13%)	32 (17%)	14 (26%)	3 (9%)
> 470 to ≤ 500 msec	6 (7%)	9 (11%)	12 (6%)	6 (13%)	1 (3%)
≥ 500 msec	2 (2%)	5 (6%)	6 (3%)	1 (2%)	0 (0%)

1 QTc increases or outliers (whether by Bazett or Fridericia correction) are combined in the analysis.
Source: Submission of July 9, 2003, pg 16, 17, and 20.

7.16.4.2 FDA Analyses of QTc Interval Changes

The FDA Biopharmaceutical Reviewer (Dr. DJ Chatterjee) was provided with the same data sets used by the Sponsor's consultant. The results of the FDA's independent analyses of the same data sets are provided in Table 95 and Table 96. The mean on-treatment increase from baseline in the abarelix group ranged from 13 to 18 msec (change in mean values) to 11 to 13 msec (mean of the individual changes from baseline) (Table 95). These changes in the abarelix group were numerically comparable to, or slightly less, than those observed in the active comparator groups.

Table 95 FDA Analyses of QTc Interval Changes (Studies ABACAS 1, 149-98-02, and 149-98-03)

Parameter (msec) [1]	Study ABACAS 1		Studies 149-98-02 and 149-98-03		
	Abarelix N = 82	Zoladex + Casodex N = 85	Abarelix N = 188	Lupron N = 46	Lupron + Casodex N = 34
Overall Population Analysis					
Mean QTc at baseline,	408	404	412	415	413
Mean QTc on treatment	426	428	425	432	423
Mean QTc change	18	24	13	17	10
Individual Analysis					
Mean QTc change	11	20	13	17	12

[1] FDA analysis by Biopharmaceutical Reviewer; correction method = Fridericia.
Source: Modified from Regulatory Briefing of July 28, 2003 (FDA Biopharmaceutical Reviewer's presentation).

The FDA's analyses of the QTc interval outliers are presented in Table 96. In ABACAS 1, the percentages of patients with a QTc increase from baseline of ≥ 60 msec or with a maximum on-treatment values of ≥ 450 or 500 msec was numerically greater in the Zoladex plus Casodex treatment group compared to the abarelix group. In Studies 149-98-02 and 149-98-03, the percentage of abarelix treated patients with a QTc increase of ≥ 60 msec was numerically comparable to that in the

Lupron and Lupron plus Casodex groups combined. The percentages of abarelix treated patients with an on-treatment QTc value of ≥ 450 msec or ≥ 500 msec, compared to that of the Lupron and Lupron plus Casodex groups combined, was numerically comparable (≥ 450 msec) or slightly greater (≥ 500 msec), respectively.

Table 96 FDA Analyses of QTc Outliers (Studies ABACAS 1, 149-98-02, and 149-98-03)

QTc value (actual or change from baseline)[1]	Number (%) of Patients				
	Study ABACAS 1		Studies 149-98-02 and 149-98-03		
	Abarelix N = 82	Zoladex + Casodex N = 85	Abarelix N = 188	Lupron N = 46	Lupron + Casodex N = 34
Change from baseline					
≥ 30 msec	17 (21%)	39 (46%)	48 (25%)	19 (41%)	10 (29%)
≥ 60 msec	1(0.5%)	4 (5%)	5 (3%)	2 (4%)	0 (0%)
On-treatment value					
≥ 450 msec	15 (18%)	19 (22%)	36 (19%)	14 (30%)	4 (12%)
≥ 500 msec	0 (0%)	5 (6%)	5 (3%)	0 (0%)	0 (0%)

[1] FDA analysis by Biopharmaceutical Reviewer; correction method = Fridericia
Source: Modified from Regulatory Briefing of July 28, 2003 (FDA Biopharmaceutical Reviewer's presentation)

Medical Officer's Comments

- *The differences between the Sponsor's analyses for outliers and the FDA's analyses may be due, at least in part, to methodologically differences. The Sponsor's outlier analysis appears to have used values that were obtained with either the Fridericia and Bazett corrections. It appears that the Sponsor identified the larger of the 2 QTc values (i.e., the Fridericia or Bazett derived value) and used this value in the outlier analysis. In contrast, the FDA analysis used only the Fridericia correction because a separate preliminary analysis indicated that this was the more appropriate correction for the raw data.*
- *For ABACAS 1, the percentage of patient with a change from baseline of ≥ 60 msec and a maximum on-treatment value of ≥ 450 msec was lower in the abarelix treatment group in both the Sponsor and FDA analyses. In Studies 149-98-02 and 149-98-03, the percentage of abarelix-treated patients with a QTc increase of ≥ 60 msec was numerically comparable to, or slightly greater than that in the comparator groups. The percentage of abarelix treated patients with an on-treatment QTc value of ≥ 500 msec was numerically slightly greater in the abarelix-treated patients.*
- *The QTc data obtained from these studies is subject to several limitations. Since QTc measurements in all treatment groups were obtained just prior to the next dosing with Study Drug, it is possible that the maximal QTc changes, if a direct effect of the Study Drugs, were greater than those observed. There also are no QTc data from this population of elderly men with prostate cancer in which subjects received either placebo or an active QTc control (i.e., a drug with a well documented effect on the QTc interval).*
- *The mechanism for the apparent effects of GnRH analogs (agonists and antagonists) on the QT interval is not known. Based on other clinical data and clinical reports [redacted], it is possible that the observed QTc changes are a consequence of the reduction of serum testosterone in the study patients, the therapeutic mechanism of action for these drugs. If so, comparable changes also would be expected after surgical castration.*

7.16.4.3 Consultation from the Division of Cardio-Renal Drug Products

The Division of Cardio-Renal Drug Products (DCRDP) was consulted regarding the QTc interval changes that were observed in Study ABACAS 1. (QTc data from Studies 149-98-02 and 149-98-03 were not available to DRUDP at the time of the consultation). In his consultation of 17 June 2003, Dr. Stockbridge made the following statements:

> "Both treatments clearly prolong repolarization, and the amount of prolongation is similar at 3 and 12 months. No attempt was made to reproduce the sponsor's calculation of a mean effect on QTcF. The reported values of 12 ms on abarelix and 18 ms on standard therapy appear to be consistent with Figure 3."
>
> "A review of these data by [the Sponsor's consultant] suggests that these data mean that abarelix poses no more, and possibly less, proarrhythmic risk than standard therapy. Such a conclusion is patently unwarranted, for several reasons. First, risk across drugs is poorly correlated with the effect on QT, and estimated relative risk across drugs that share nothing in terms of structure or function is particularly difficult to defend. Second, the only QT data available were obtained at the interdosing interval. Effects at peak plasma levels of parent drugs or metabolites cannot be inferred; the integral risk may be much higher than is suggested by QT data at trough. Information on the time course of QT effects after a dose should be obtained."
>
> "At the end of the day, if a case can be made that abarelix confers a substantial clinical benefit in its target population, some proarrhythmic risk should be acceptable. However, if the clinical benefit is short of mortality, it would appear that a more complete characterization should be obtained, specifically with respect to changes in QTcF as a function of time, and, given the difficulty with enforcing phase IV commitments, such information should be obtained and reviewed prior to approval."

7.16.4.4 Analyses across All Abarelix Studies for Adverse Events Potentially Associated with QT Prolongation

To assess the clinical significance of the observed changes in the QTc interval, the Sponsor was asked by the primary Medical Reviewer to conduct a review of all abarelix studies for adverse events potentially associated with QT prolongation. Based on a list of adverse event preferred terms that was provided by the Medical Reviewer, and further expanded by the Sponsor, the Sponsor conducted the requested review (Submission of 17 July 2003).

A total of 91 of 1,916 patients treated with abarelix (4.7%) reported at least one adverse event (110 total events) that coded to the FDA and PRAECIS composite preferred term list. For patients treated with comparator therapies that consisted of Lupron alone, Lupron plus Casodex, and Zoladex plus Casodex, a similar proportion, 27 of 581 patients (4.6%), reported at least one such adverse event. The number of adverse events expressed per 100 patient-years of exposure to treatments also was comparable between the abarelix-treated patients and comparator-treated patients. Across the 1,916 abarelix-treated patients, there were 1,259.9 patient-years of exposure, resulting in 8.7 adverse events per 100 patient-years of exposure to abarelix. Across the 581 comparator-treated patients, there were 331.3 patient-years of exposure, resulting in 8.8 events per 100 patient-years of comparator therapies.

Reported adverse events (expressed as preferred terms) that could have been a consequence of prolongation of the QT interval and which were identified in the Sponsor's review included the following terms: arrhythmia, arrhythmia ventricular, cardiac arrhythmia, ECG abnormal, palpitation,

palpitations, QT prolonged, tachycardia ventricular, cardiac arrest, syncope, hypotension, hypotension NOS, postural hypotension, seizure, grand mal seizure, TIA, and transient ischaemic attack.

Events that coded to cardiac arrest occurred for 4 patients treated with abarelix, all during rollover studies. Three of these events, on study Days 612, 629, and 1219, resulted in death. The fourth patient had a cardiac arrest on study Day 708 but recovered with sequelae. In all 4 cases, any relationship to abarelix was excluded by the investigator. The Sponsor also reviewed all deaths in the clinical trials for cases of death that were coded to a preferred term that was not on the composite list of preferred terms potentially associated with QT prolongation, but for which the source information indicated that such an event might have occurred. One additional abarelix-treated patient and one comparator patient were identified. Table 97 (prepared by the Sponsor) provides a summary of the clinical events preceding the event of cardiac arrest or other cardiac event.

Adverse events (other than the term "QT prolonged") potentially associated with QT prolongation among patients with a QTc change >60 msec from baseline were reported for 2 patients. One patient in the comparator group in ABACAS 1 (Pt. No. 2941-0086, QTc change of 101 msec) had an adverse event that coded to "TIA." One patient in the abarelix group in Study 149-98-03 (Pt. No. 012-3082, QTc change of msec 62 msec) had an adverse event that coded to ventricular arrhythmia.

Medical Officer's Comments

- *Abarelix Pt. No. 012-3082 with a QTc change of msec 62 msec and a reported adverse event of ventricular arrhythmia (noted above) had a long history of preexisting ischemic heart disease and was reported to have multi-vessel coronary artery disease. Exercise testing revealed "complex ventricular ectopy with inducible ventricular tachycardia."*
- *The numeric imbalance observed in Table 97 (5 of the 6 patients were treated with abarelix) may be due, in part, to the greater number of patients exposed to abarelix (n = 1,916) than to comparator (n = 581). Two of the 5 abarelix-treated patients listed in Table 97 (Nos. 001-2601 and 745-0274) also had a well documented history of preexisting cardiac disease. Two of the 3 patients without a know history of cardiac disease (Nos. 441-4036 and 438-4028) had advanced prostate cancer at entry (Stage D1 or D2) and died after 612 and 274 days of treatment, respectively. None of the cardiac adverse events for the patients listed in Table 97 were attributed to treatment with Study Drugs by the Investigators.*

Table 97 Clinical Information for Patients with Death Attributed to Cardiac Arrest or Other Cardiac Event

Patient	Age at Entry (years)	Study	Study Drug	Exposure (days) to Event	Prior Medical History	Pre-Terminal On-study AE of Note	Terminal Event	Event Code	Relationship to Study Drug
438-4028	71	149-98-04/ 149-99-04	Abarelix	612	D1 prostate cancer, Gleason 8; hydro-nephrosis, bladder outlet obstruction	Congestive heart failure	Found dead in bed at home	Cardiac arrest (fatal)	Excluded
001-2601	81	149-97-04/ 149-99-04	Abarelix	1216	D2 prostate cancer; cardiac bypass x 2, angina, coronary artery disease	Syncope 24 days prior to death with no acute ECG changes	At home stopped breathing-fell over	Cardiac arrest (fatal)	Excluded
745-0274	81	ABACAS 1 and Extension	Abarelix	629	Arrhythmia; pacemaker; coronary insufficiency & multiple cardiac medications		Cardiac arrest	Cardiac arrest (fatal)	Excluded
441-4036	94	149-98-04/ 149-99-04	Abarelix	274	D2 prostate cancer with 7 bony metastases		Died at home, cardiorespiratory arrest secondary to progression of metastatic prostate cancer	Metastases NOS (fatal)	Excluded
022-2119	81	149-98-02	Lupron	308		Near-syncope, respiratory failure, & Myocardial infarction 3 days before death	Myocardial infarction (fatal) and emphysema	Myocardial infarction (fatal)	Excluded
031-4674	86	149-97-04	Abarelix	704	Dementia	Congestive heart failure, respiratory failure	Cardiac arrest: Found unres-ponsive, pupils dilated, was resuscitated & recovered with sequelae	Cardiac arrest (non-fatal)	Excluded

Table prepared by Sponsor. Information not confirmed by Medical Reviewer.
Source: Submission of 17 July 03, Table 2, pg. 6 of 8.

7.16.4.5 Medical Officer's Overall Assessment of Risk related to QT Interval Prolongation in Abarelix-Treated Patients

Under the conditions of data collection in the controlled clinical trials, the observed mean increases from baseline in the QTc interval were similar in the abarelix-treated patients and in the patients treated with standard therapy (Lupron, Lupron plus Casodex, and Zoladex plus Casodex). Similarly the numbers of patients with increases in the QTc interval of >30 msec and >60 msec from baseline was similar in the abarelix treatment patients and the standard therapy patients. Overall, the percentages of patients for whom an adverse event, potentially related to prolongation of the QT interval, was reported was similar in the abarelix and comparator treatment groups (4.7% and 4.6%, respectively).

With the possible exception of the information presented in Table 97, there were no data submitted in NDA 21-302 that suggest that treatment with abarelix may pose a greater cardiac risk than treatment with presently approved GnRH therapies, with or without concomitant nonsteroidal antiandrogens. The numeric imbalance observed in Table 97, (5 of the 6 patients were treated with abarelix) may be due, in part, to the greater number of patients exposed to abarelix (n = 1,916) than to comparator (n = 581). In addition, 2 of the 5 abarelix-treated patients listed in the Table (Nos. 001-2601 and 745-0274) had a history of preexisting cardiac disease. The Sponsor has proposed the following statement in the Warnings Section of the label: C

DRAFT

] This warning is appropriate and should be included in the product label.

7.17 Risk Management Plan (RPM)

7.17.1 Submission of 25 February 2003

The Complete Response submitted on 25 February 2003 included a RMP to address DRUDP's request for a plan that would accomplish the following three objectives: (1) ensure that abarelix is used only in the indicated treatment population; (2) ensure that healthcare professionals are aware of the safety profile of abarelix and that they have the ability to treat any events that emerge following abarelix treatment, i.e., immediate-onset systemic allergic reactions; and (3) alert healthcare professionals to the potential for fluctuating testosterone levels and suggest periodic laboratory tests to monitor testosterone and PSA levels beyond 6 months of treatment to assess efficacy.

The focus of the proposed RMP, according to the Sponsor was "to provide a risk communication message delivered through a variety of means including proper sales detailing, product labeling, product packaging, an open-access website, a toll-free telephone number for medical information, research publications, advertising, and other educational material." The proposal also stated that "a survey of prescribing oncologists and urologists will be conducted within 6 months following product launch to assess physicians' prescribing patterns."

Medical Officer's Comments

- *The Sponsor's proposed RMP submitted on 25 February 2003 contained several of the necessary components for an effective RMP but (1) did not provide sufficient detail as to how several aspects of the program would be conducted, (2) was not sufficiently restrictive in many areas, and (3) did not address several critical areas.*
- *Although the Sponsor's proposed RMP included a number of activities that would help to diminish the risk associated with abarelix treatment, sufficient details were missing from this proposal to make any definitive conclusions about its likely overall effectiveness. For example, a minimum time for observing patients postdosing (e.g., 30 minutes) and a specific schedule for monitoring serum testosterone concentrations needed to be added to the proposed label. The*

Sponsor also needed to provide additional information regarding the intervention plan and how they would be evaluating that plan, including a timeline that went beyond the first 6-months of marketing.

- *The following paragraph, taken from the DDRE Consultation of 13 June 2003, summarizes the major deficiencies of the proposed RMP submitted on 25 February 2003:*

  "The following information is lacking from the RMP: a clear definition of what is the "clinically appropriate" time period for monitoring after treatment administration (referred to in sections 1.2 and 1.3.); sufficient data to support the sponsor's conclusions that the majority of practicing urologists are equipped to treat immediate-onset allergic reactions and that most patients will be receiving their treatment in a hospital or academic setting where equipment will be available for emergency response to life threatening hypersensitivity reactions; a definition of the planned sample size and the kind of information that will be collected in the survey of prescribing oncologists and urologists; a description of how practitioners will be made aware of the toll-free telephone number that is to be used for reporting adverse events; a description of how urologists and oncologists who see the "highest number of symptomatic patients" will be identified; and whether the sponsor intends to assess physician prescribing patterns on a national level and if so, the intended methodology. Finally, there is no information provided as to how healthcare workers will be evaluated to determine whether they are periodically monitoring for fluctuating testosterone levels. The sponsor should be asked to provide additional information regarding the intervention plan and how it will be evaluated. A timeline that extends beyond the first 6-months of marketing should be provided. Although the proposed RMP includes a number of activities that may diminish the risk associated with abarelix treatment, sufficient details are missing from this proposal to draw any definitive conclusions."

7.17.2 Submission of 8 August 2003

Following further discussion with DRUDP, the Sponsor submitted a revised RMP (Amendment 66) on August 8, 2003. The most significant addition to the revised RMP was inclusion of a restricted distribution program for abarelix to maximize the likelihood that the drug would be used to treat only those patients for whom the risk/benefit ratio was acceptable (i.e., patients with advanced symptomatic prostate cancer in whom the benefits of treatment would outweigh the risks). Other new components of the revised RMP included (1) a Prescriber's Agreement and (2) a Hospital /Pharmacy /Group Program Agreement Statement.

Medical Officer's Comments

- *Although the submission of 8 August 2003 included a general plan for a restricted distribution program, it again lacked sufficient detail. Most importantly, it did not describe how the program would be monitored to ensure that it was functioning as intended and it did not provided details as to what remedial actions would be taken if needed.*
- *Since the submission of 8 August 2003, the proposed RMP program has been further refined and will include, in addition to restricted distribution, (1) a Physician Attestation of Qualifications and Acceptance of Responsibilities, (2) a Hospital Pharmacies Acceptance of Responsibilities, (3) and a Patient Information Sheet that requires that the patient acknowledge, by signature, that he has read and understands the basis for his being treated with abarelix and the risks associated with the treatment (see Section 7.20 for discussion of final RMP).*

7.18 Safety Consultations

Three Divisions/Offices were consulted regarding safety-related issues. These were (1) Division of Pulmonary and Allergy Drug Products (DPADP) regarding serious allergic reactions; (2) Division of Cardio-Renal Drug Products (DCRDP) regarding changes in the QT interval; and (3) Division of Drug Risk Evaluation (DDRE) regarding the Risk-Management Plan.

7.18.1 Consultation from Division of Pulmonary and Allergy Drug Products (DPADP)

The following is the Executive Summary of Dr. Lee's Consultation of July 2, 2003:

> "In this submission, the sponsor has provided results of skin tests and in vitro tests for anti-abarelix IgE antibody and anti-CMC IgE and IgG antibodies in patients who had allergic reactions to abarelix and in appropriate control patients. The sponsor has also provided a risk management program to address these reactions.
>
> The sponsor's skin testing data do not provide sufficient information to assess the potential for predicting patients who may be at risk for immediate allergic reactions. The skin tests indirectly support the conclusion that the immediate onset reactions noted during the abarelix clinical development program were of an anaphylactoid or non-immune etiology.
>
> The in vitro tests revealed no meaningful differences in abarelix-specific IgE, CMC-specific IgE or IgG, total IgE, or total IgG levels between abarelix-treated patients and active control-treated patients or between patients who had allergic reactions and those who did not. These data suggest that the reactions noted in the clinical development program in abarelix-treated patients do not have an IgE or IgG-mediated etiology, and also provide indirect evidence that the reactions are anaphylactoid in nature.
>
> An updated estimate of the frequency of immediate onset allergic reactions in abarelix-treated patients in the sponsor's clinical development program was 1.1%. There were no such reactions noted in patients treated with active control. The frequency of immediate onset allergic reactions with hypotension or syncope was 0.5% in abarelix-treated patients. There were no immediate onset allergic reactions with hypotension or syncope in patients treated with active control. Updated estimates of the rates of immediate allergic reactions and immediate allergic reactions associated with hypotension or syncope after various periods of exposure may be found in the statistics review of this submission [NDA 21-320, N000 AZ, 2/25/03, Kate Meaker, MS].
>
> The sponsor's risk management plan appears to be acceptable from the clinical standpoint. The sponsor has narrowed the proposed indication to patients with advanced symptomatic carcinoma of the prostate who have impending neurologic compromise, urinary tract obstruction, and/or bone pain from prostate cancer skeletal metastases requiring narcotic analgesia. The new narrowed proposed indication focuses on a population in which the risk of immediate allergic reactions may be acceptable. The sponsor's plan to communicate appropriate risk and benefit information to healthcare providers and patients is comprehensive. The sponsor's plan to monitor the success of their risk management plan is appropriate from the clinical perspective. In order to further characterize the etiology of these of immediate onset allergic reactions, and as part of the risk management plan, consideration should be given to requesting the sponsor make a Phase 4 commitment to perform skin testing and in vitro testing of a defined number of patients who have such reactions to abarelix in the post-approval period."

Medical Officer's Comments

- *The primary Medical Reviewer concurs with Dr. Lee's assessment and recommendations with one exception. The original Risk Management Program as proposed by the by the Sponsor in the submission of February 25, 2003 is not adequate or acceptable. Although the original proposal*

contained many of the necessary components, the overall proposal was incomplete (see comments from the DDRE review of 13 June 03 that are summarized in Section 7.17.1).

- *The Sponsor has made a Phase 4 commitment to perform skin testing and in vitro testing of a defined number of patients who have immediate onset systemic allergic reactions to abarelix in the post-approval period.*

7.18.2 Consultation from Division of Cardio-Renal Drug Products (DCRDP)

Specific comments/recommendations from the DCRDP regarding the clinical significance of changes in the QT interval observed in patients treated with abarelix are summarized in Section 7.16.4.3.

7.18.3 Division of Drug Risk Evaluation (DDRE)

Specific comments/recommendations from the DDRE regarding the adequacy of the Sponsor's original RMP proposal are summarized in Section 7.17.

7.19 Overall Assessment of Safety

7.19.1 Adequacy of Patient Exposure x

A total of 1397 prostate cancer patients were exposed to the depot formulation of abarelix. Of these 1397 patients, 1154 patients received the registration dose (100 mg for both induction and maintenance of castration) and 243 patients received nonregistration doses. Among patients receiving the registration dose of abarelix, 87 were studied in a non-IND clinical trial (ABACAS 1 conducted entirely in Europe). Including cumulative exposure in the safety extension studies, 829 patients were exposed to the registration dose for 6 months, 327 were exposed for at least 1 year, and 113 were exposed for at least 2 years.

Of the 1397 patients who received one or more doses of abarelix, 81 patients had advanced, symptomatic prostate cancer (the indicated population for abarelix). Among these 81 patients, 61 patients were exposed to abarelix for ≥24 weeks, 33 were exposed for ≥48 weeks, and 13 were exposed for ≥108 weeks.

Medical Officer's Comments

- *The size of the clinical program was adequate for this new molecular entity. The number of patients with advanced symptomatic prostate cancer who were treated with abarelix in Study 149-98-04, however, was small (n = 81). In spite of the limited number of patients with advanced symptomatic prostate cancer, the Sponsor has provided sufficient data to conclude that abarelix can be administered to these patients with little or no risk of causing a testosterone induced clinical flair. This conclusion is based on both the clinical data obtained in Study 149-98-04 and the serum testosterone concentration data from the controlled clinical trials in which none of the 348 patients treated with abarelix experienced a surge of testosterone following the onset of treatment.*
- *Although only 81 patients in the clinical development program had documented, clinically advanced symptomatic prostate cancer (the indicated population), this reviewer believes that the general safety data obtained from the patients enrolled in the U.S. controlled clinical trials (n = 735) and the supportive trials (n = 338) are applicable to the indicated population. Protocol-designated safety assessments (both clinical and laboratory) were performed monthly in all of the clinical trials. The safety assessments were appropriate and adequate with one exception. The exception was that the Sponsor did not initially investigate further or follow up with patients who had experienced immediate postdosing systemic allergic reactions. However,*

subsequent to NDA 21-320 not being approved in June 2001, the Sponsor conducted additional studies to obtain additional information about the mechanism(s) underlying the immediate allergic reactions.

7.19.2 Safety Findings

7.19.2.1 Indicated Patient Population (Patients with Advanced Symptomatic Prostate Cancer)

All patients in Study 149-98-04 avoided orchiectomy through study Day 85, the protocol defined primary efficacy endpoint. No patient (with one possible exception who reported severe bone pain) had a clinically significant adverse event suggestive of a testosterone-induced clinical flare following the onset of treatment. Six of 81 patients (7%) died during their participation in Study 149-98-04 and an additional 4 patients died during their participation in the safety extension study. None of the deaths was attributed to treatment with abarelix. Excluding premature withdrawals due to disease progression (n = 10) and deaths, 3 of 81 patients (4%) in Study 149-98-04 were withdrawn prematurely because of an adverse event. The adverse event in each instance was a systemic allergic reaction that occurred within minutes of dosing on Study Days 15 (urticaria), 29 (urticaria and pruritus), and 141 (syncope and hypotension), respectively. Of the spontaneously reported adverse events, hot flashes, sleep disturbances due to hot flashes, pain, breast enlargement, breast pain, back pain, constipation, and peripheral edema were the most frequently reported events.. Among patients with ALT and AST values that were not > ULN at baseline, 25 of 75 (33%) and 21 of 74 (28%) had increases to >ULN while on-treatment. Two patients (ALT) and 3 patients (AST) had elevations > 2.5 x ULN, respectively.

Abarelix, without concomitant antiandrogen therapy, can be administered to men with advanced symptomatic androgen dependent prostate cancer (the indicated patient population) with little, or no risk of a testosterone-induced clinical flare.

7.19.2.2 Primary Controlled Safety Studies (Men with Less Advanced Prostate Cancer)

General Safety Findings

The types of reported adverse events and the proportion of patients reporting them in the controlled clinical trials were compatible with the study population (men with carcinoma of the prostate with a median age of > 70 years). For most categories of adverse events, the reported frequencies were similar in the abarelix and active control groups. The percentages of patients that were withdrawn because of treatment-related adverse events were similar in the Lupron and abarelix treatment groups and higher in the Lupron plus Casodex group. Overall, 5 of 284 (1.8%) patients in the Lupron group, 6 of 83 (7.2%) patients in the Lupron plus Casodex group and 19 of 735 (2.6%) patients in the abarelix group were withdrawn because of a treatment-related adverse event.

Changes in safety laboratory values also were generally similar across the treatment groups with the exception of increases in transaminases (see below) and triglycerides. Other than these exceptions, there were no remarkable or consistent differences in mean changes from baseline values in the pooled hematology and chemistry values from the 3 primary safety studies. Isolated, intermittent, or extreme changes for some measurements at some assessment times were noted, but no consistent patterns suggestive of increased toxicity in the abarelix groups were observed. Mean fasting serum triglyceride levels were numerically higher by 10-15 mg/dL in the abarelix group compared to the Lupron group in the controlled safety studies. This increase in triglycerides, although not desirable, is not a significant safety concern in the population of men to be treated with abarelix.

Patient Deaths

In the controlled safety studies, a total of 12 patients died (1 in the Lupron group and 11 in the abarelix group), either during the treatment period (within 28 days of the last dose of Study Drug) or during the posttreatment follow up period. Although the proportion of abarelix-treated patients in the controlled studies who died (11 of 735, 1.4%) was greater than that of the active control-treated

patients (1 of 367, 0.3%), it is likely, as reported by the Investigators, that none of these deaths was a result of treatment with abarelix. The causes of death in the abarelix-treated patients appear to be compatible with those that would be expected in a population of elderly men with carcinoma of the prostate. Of the 11 deaths in the abarelix-treated patients 3 cases (2 cases of pulmonary carcinoma and 1 case of pancreatic carcinoma) were very unlikely to have been related to treatment with abarelix, and 2 cases were related to progression of prostate cancer. Of the remaining 6 deaths, 2 occurred > 50 days after the patient's last dose of abarelix. The remaining 4 deaths all occurred on-treatment (i.e., within 28 days of the last dose of abarelix). These 4 deaths were attributed to an intracranial hemorrhage, a myocardial infarction, an empyema of the right lung, and chronic obstructive lung disease, respectively. The causes of death in the abarelix-treated patients appear to be compatible with those that would be expected in a population of elderly men with carcinoma of the prostate.

Safety Issues of Particular Concern

Immediate onset systemic allergic reactions. Patients treated with abarelix are at greater risk of having an immediate onset, serious systemic allergic reaction than patients treated with Lupron or Zoladex (see Section 7.16.2). In the clinical development program for abarelix (all clinical trials with abarelix including investigator initiated studies), 16 of 1414 patients (1.1%) had a systemic allergic reaction within 1 hour of dosing. In 7 of these patient (0.5% of total patients), the allergic reaction included syncope and/or hypotension. None of the patients treated with Lupron, Lupron plus Casodex, or Zoladex plus Casodex had an immediate onset systemic allergic reaction.

Decreased effectiveness in terms of suppression of serum testosterone with continued dosing. In the 3 primary controlled clinical trials, the capacity of abarelix to achieve medical castration (i.e., serum testosterone concentration ≤ 50 ng/dL) by Day 29 and maintain medical castration through 1 year (Day 365) was inferior to that of Lupron or Lupron plus Casodex (see Section 6.12.3.2 and Section 6.12.3.3). This issue will need to be addressed in labeling and will require regular monitoring of serum testosterone concentrations.

Prolongation of the QT Interval. Treatment with either abarelix or a GnRH agonist (Lupron, Lupron plus Casodex, or Zoladex plus Casodex) prolonged the mean Fridericia-corrected QT interval by > 10 msec from baseline in all treatment groups (see Section 7.16.4). In approximately 20 to 40% of patients in the abarelix and GnRH agonist treatment groups, there were either changes from baseline QTc of >30 msec or end-of-treatment QTc values exceeding 450 msec. It is unclear whether these changes were directly related to study drugs, to androgen deprivation therapy, or to other variables.

Hepatic toxicity. In the 3 primary controlled clinical trials, a greater percentage of abarelix-treated patients had a shift in transaminase values from not > ULN at baseline to > ULN at the end of treatment than in the active comparator groups. A small percentage of these increases were of clinical significance in both groups. The percentages of abarelix-treated patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 8.2% and 1.8%, respectively. In the active comparator groups combined, the percentages of patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 6.6% and 1.1%, respectively. The percentages of patients reporting serum AST >2.5 times upper limit of normal or >200 U/L were similar in the abarelix and active comparator groups.

Conclusion

Based on the observed safety profile of abarelix in clinical trials conducted to date, the benefits of abarelix treatment out weight the risks for men with advanced symptomatic prostate cancer in whom treatment with a GnRH agonist is not appropriate and who refuse orchiectomy and who have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from

skeletal metastases persisting on narcotic analgesia. The benefits of abarelix treatment do not outweigh the risks for men with clinically less advanced prostate cancer.

7.20 Risk Management Program

The abarelix Risk Management Program, agreed to by both DRUDP and the Sponsor, includes the following components:

- Labeling that includes a boxed warning that addresses:
  - the risk of immediate systemic allergic reactions that may occur following any administration of abarelix, including the first dose and the need to observe patients for 30 minutes after each administration of abarelix
  - the decrease in effectiveness in suppressing serum testosterone concentrations to castrate levels that occurs in some patients with continued dosing and the need to measure serum testosterone concentrations immediately prior to dosing on Day 29 and every 8 weeks thereafter in all patients
- A restricted distribution program for abarelix
- An agreement for hospital pharmacists confirming their participation in the program and the actions required prior to dispensing the drug
- Limiting prescribers of abarelix to only those physicians who have enrolled in the Plenaxis™ Plus Program (Plenaxis™ User Safety Program), based on their attestation of medical qualifications and acceptance of prescribing responsibilities
- A Patient Information Sheet that requires the patient to acknowledge by signature that he has read, understands and agrees with all the statements contained in the Information Sheet
- Expedited reporting of specific adverse events (e.g., immediate allergic reactions) that would not otherwise require expedited reporting because they are listed in labeling
- Measures to actively monitor and evaluate the risk management program
- A physician/ healthcare provider education program.

8 DOSING, REGIMEN, AND ADMINISTRATION

The presently recommended dose and dosing regimen for abarelix for the palliative treatment of advanced symptomatic prostate cancer, based on the clinical trials conducted by the Sponsor, is 100 mg by IM injection on treatment days 1, 15, and 29 and every 28 days thereafter. This dose of abarelix is effective in suppressing serum concentrations of testosterone to ≤ 50 ng/dL by treatment Day 29 and maintaining serum testosterone at these concentrations through treatment Day 85 in approximately 90% of men. However, with continued dosing the effectiveness of abarelix, in terms of maintenance of suppression of serum testosterone, decreases. This decrease in effectiveness is most noticeable at the end of each 28-day dosing cycle (i.e., just before the next dose of abarelix) and in men who weigh more than 225 pounds.

Medical Officer's Comments

- *A higher dose of abarelix, a shorter dosing interval (i.e., more frequent than every 28 days), or an alteration in the release profile of the depot formulation (i.e., a greater percentage of release during days 22-28 after dosing) would likely reduce the observed decrease in efficacy.*

- *The Sponsor should investigate the changes suggested above regarding dose, dosing regimen, and formulation to improve the long-term effectiveness of abarelix.*
- *This issue of decreased effectiveness will need to be addressed in labeling and will require regular monitoring of serum testosterone concentrations. The decrease in effectiveness is not of sufficient magnitude as to preclude recommending approval of abarelix for the indicated population of men with advanced, symptomatic prostate cancer who refuse surgical castration. Since treatment of such men with a GnRH agonist (the only alternative medical therapy), even in conjunction with an antiandrogen, poses a significant risk of inducing a flare in their symptoms of advanced prostate cancer, the risk of decreased effectiveness with continued dosing in some patients is warranted.*

9 USE IN SPECIAL POPULATIONS

Men. Abarelix is to be used only for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH (GnRH) agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. This indication will limit its on-label use to men, primarily elderly men. In additional, abarelix will be available only (1) through a limited distribution program and (2) only to physicians who have enrolled in the Sponsor's Risk Management Program, in which enrollment is based on physician attestation of (a) qualifications to diagnosis and manage men with advanced prostate cancer and (b) acceptance of prescribing responsibilities.

The sponsor performed standard subset safety and efficacy (pharmacodynamic) analyses for the data from the controlled safety studies (Studies 149-98-02, 149-98-03 and 149-99-03) based on race (African American and non-African American) and age (<65, 65-74, and >75, safety analyses only). No obvious differences across these groups were identified. However, the total numbers of African American patients and patients less than 65 years of age included in these analyses were small. According to the Biopharmaceutics Reviewer, race did not appear to have a clinically meaningful effect on the pharmacokinetics of abarelix in men in the clinical trials. However, the power to detect differences was low because of the small numbers of non-Caucasian subjects.

[ ]

Labeling for abarelix should clearly state that it should not be used in women.

Children. Abarelix has not been studied in children. Based on the known pharmacology of abarelix and its safety profile in adults, it should not be administered to children.

Patients with renal or hepatic impairment. The pharmacokinetics of abarelix was not evaluated in patients with renal or hepatic impairment.

10 CONCLUSIONS AND RECOMMENDATIONS

10.1 Risk-Benefit Assessment

10.1.1 Benefits of Treatment with Abarelix Compared to Other Medical Therapeutic Options

Prostate cancer that has advanced to the stage where it is no longer curable by either radical prostatectomy or radiation therapy is generally treated by medical or surgical castration. At the

present time, medical castration by GnRH agonistic analogs (e.g., Lupron or Zoladex), with or without an antiandrogen, is more commonly used in the U.S. for the palliative treatment of prostate cancer than surgical castration. In contrast to surgical castration, which results in a rapid (within days) decrease in serum testosterone concentrations to ≤ 50 ng/dL, 3-4 weeks of treatment with a GnRH analog is generally required before complete suppression of serum testosterone concentrations is obtained.

Treatment with a GnRH agonist, in contrast to surgical castration, also initially results in a significant, albeit temporary (1 to 2 week), increase in testicular androgen secretion, commonly referred to as a "testosterone surge." The initial rise in serum testosterone may cause a worsening of prostate cancer symptoms referred to as a "clinical flare." Most commonly, the immediate consequence of this initial increase in circulating testosterone levels in men with metastatic disease is an increase in bone pain. Less frequently, more serious adverse events can occur, including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death. For these reasons, concomitant antiandrogen therapy is generally administered for at least the first month of therapy when GnRH agonists are used to treat men with advanced symptomatic prostate cancer. Even with concomitant antiandrogen therapy, GnRH agonists must be used with caution in patients presenting with large local lesions, impending ureteral or bladder neck outlet obstruction, and severe skeletal pain requiring the use of narcotic analgesics. Antiandrogens also have their own spectrum of adverse effects, and they may not completely block the adverse consequences of a GnRH-induced testosterone surge. Consequently, GnRH agonists, even if administered with concomitant antiandrogen therapy, are generally considered inappropriate therapy for men with vertebral or epidural metastases or neurologic symptoms of spinal cord compression.

Abarelix, in contrast to GnRH agonists such as Lupron or Zoladex, is a true GnRH antagonist that is devoid of any LH and FSH releasing activity. Consequently, administration of abarelix more rapidly inhibits the secretion of LH and testicular testosterone, without initially producing an increase in serum testosterone concentrations. Consequently, abarelix, as was shown in clinical Study 149-98-04, can be used for the palliative management of advanced prostate cancer with little, or no risk of causing an exacerbation of the patient's signs or symptoms of prostate cancer. However, for the patient who finds orchiectomy to be an acceptable treatment option, abarelix provides no therapeutic advantage and is less safe.

10.1.2 Risks of Treatment with Abarelix Compared to Other Medical Therapeutic Options

Immediate onset systemic allergic reactions. Patients treated with abarelix are at greater risk of having an immediate onset, serious systemic allergic reaction than patients treated with Lupron or Zoladex (see Section 7.16.2). In the clinical development program for abarelix (including investigator initiated studies), 16 of 1414 patients (1.1%) had a systemic allergic reaction within 1 hour of dosing. In 7 of these patient (0.5% of total patients), the allergic reaction included syncope and/or hypotension. None of the patients treated with Lupron, Lupron plus Casodex, or Zoladex plus Casodex had an immediate onset systemic allergic reaction.

Decreased effectiveness in terms of suppression of serum testosterone with continued dosing. Abarelix is effective in suppressing serum concentrations of testosterone to ≤ 50 ng/dL by treatment Day 29 and maintaining serum testosterone at these concentrations through treatment Day 85 in approximately 90% of men. However, with continued dosing, the effectiveness of abarelix, in terms of maintenance of suppression of serum testosterone, decreases in some men (see Section 6.12.3.2 and Section 6.12.3.3).

Prolongation of the QT Interval. Treatment with either abarelix or a GnRH agonist (Lupron, Lupron plus Casodex, or Zoladex plus Casodex) prolonged the mean Fridericia-corrected QT interval by > 10 msec from baseline in all treatment groups (see Section 7.16.4). In approximately 20 to 40% of patients in the abarelix and GnRH agonist treatment groups, there were either changes from baseline

QTc of >30 msec or end-of-treatment QTc values exceeding 450 msec. It is unclear whether these changes were directly related to study drugs, to androgen deprivation therapy, or to other variables.

Hepatic toxicity. In the 3 primary controlled clinical trials, a slightly greater percentage of abarelix-treated patients had a shift in transaminase values from not > ULN at baseline to > ULN at the end of treatment than in the active comparator groups. A small percentage of these increases were of clinical significance in both groups. The percentages of abarelix-treated patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 8.2% and 1.8%, respectively. In the active comparator groups combined, the percentages of patients reporting serum ALT values >2.5 times upper limit of normal or >200 U/L were 6.6% and 1.1%, respectively. The percentages of patients reporting serum AST >2.5 times upper limit of normal or >200 U/L were similar in the abarelix and active comparator groups.

10.1.3 Overall Risk-Benefit Assessment

In contrast to GnRH agonists, abarelix suppresses serum testosterone concentrations to castrate levels (i.e., ≤ 50 ng/dL) without initially producing a "surge" in serum testosterone concentrations. This feature of abarelix is of significant clinical benefit to certain patients with advanced symptomatic prostate cancer. These patients are those in whom treatment with a GnRH agonist is not appropriate and who refuse surgical castration, and who have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. For these patients, the benefits of abarelix therapy outweigh the risks.

However, for most patients with prostate cancer, namely those with less advanced disease, the risks associated with abarelix treatment, compared to those associated with GnRH agonist treatment, are not offset by the benefits. Therefore, the labeled indication for abarelix should be for the palliative treatment of men with advanced symptomatic prostate cancer, in whom GnRH agonist therapy is not appropriate and who refuse surgical castration and who have one or more of the 3 signs or symptoms listed above.

10.2 Proposed Labeling

The Package Insert (label) originally proposed by the Sponsor was extensively revised during the review process. Among the most important changes to the label were the following:

1. An expanded boxed and bolded warning that addresses the issues of (1) immediate systematic allergic reactions, (2) who can prescribe abarelix (i.e., limited distribution), (3) the specific indication for abarelix, and (4) decreasing efficacy in some patients with continued treatment. The boxed warning is as follows:

- Immediate-onset systemic allergic reactions, some resulting in hypotension and syncope, have occurred after administration of Plenaxis™. These immediate-onset reactions have been reported to occur following any administration of Plenaxis™, including after the initial dose. The cumulative risk of such a reaction increases with the duration of treatment (see WARNINGS). Following each injection of Plenaxis™, patients should be observed for at least 30 minutes in the office and in the event of an allergic reaction, managed appropriately.
- Only physicians who have enrolled in the Plenaxis™ Prescribing PLUS Program (Plenaxis™ User Safety Program, based on their attestation of qualifications and acceptance of prescribing responsibilities, may prescribe Plenaxis™ (See DOSAGE AND ADMINISTRATION and HOW SUPPLIED).
- Plenaxis™ is indicated for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH agonist therapy is not appropriate, and who refuse surgical castration and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia.
- The effectiveness of Plenaxis™ in suppressing serum testosterone to castrate levels decreases with continued dosing in some patients (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Effectiveness beyond 12 months has not been established. Treatment failure can be detected by measuring serum total testosterone concentrations just prior to administration on Day 29 and every 8 weeks thereafter (see WARNINGS).

2. Specific information as to the percentages of patients who attained and maintained medical castration (no serum testosterone > 50 ng/dL) just prior to dosing by Day 29 and every 28 days thereafter through Day 365.
3. Elimination of pharmacodynamic data that suggested (without substantiation) that treatment with abarelix would provide benefits for prostate cancer patients beyond those that would be derived from treatment with a GnRH analog.
4. Addition of cumulative risk rates (and 95% confidence intervals) for immediate systemic allergic reactions.

10.3 Recommendations Regarding Approval

10.3.1 Approvability

It is recommended that abarelix (Plenaxis™) be approved for the palliative treatment of men with advanced symptomatic prostate cancer, in whom LHRH (GnRH) agonist therapy is not appropriate and who refuse surgical castration, and have one or more of the following: (1) risk of neurological compromise due to metastases, (2) ureteral or bladder outlet obstruction due to local encroachment or metastatic disease, or (3) severe bone pain from skeletal metastases persisting on narcotic analgesia. It is further recommended that (1) abarelix be available only through a restricted distribution program and (2) only physicians who have enrolled in the Plenaxis™ PLUS Program (Plenaxis™ User Safety Program), based on their attestation of qualifications and acceptance of prescribing responsibilities, may prescribe abarelix.

10.3.2 Basis for Recommendation regarding Approvability (Risk/Benefit Assessment)

No hormonal therapy for the management of advanced prostate cancer is more effective than surgical orchiectomy. The goal of medical hormonal therapy is to reduce serum testosterone concentrations to ≤ 0.5 ng/dL (i.e., testosterone levels comparable to those observed following orchiectomy). Treatment of prostate cancer with a GnRH agonist (e.g., leuprolide) initially increases serum testosterone concentrations for 1–2 weeks before reducing serum testosterone concentrations to castrate levels. The initial rise in serum testosterone may cause a worsening of the signs or symptoms