Table 38. Clinically Notable Chemistry Values (Studies 149-98-02, 149-98-03, 149-99-03) [1]

	Treatment Group								
	Lupron (N=284)			Lupron + Casodex (N=83)			Abarelix (N=735)		
	Eval	Experienced[2]		Eval	Experienced		Eval	Experienced	
	n	n	(%)	n	n	(%)	n	n	(%)
Serum sodium									
<125 mEq/L	281	1	(0.3)	83	0		732	0	
>155 mEq/L	281	6	(2.1)	83	1	(1.2)	732	12	(1.6)
Serum potassium									
<3.0 mEq/L	281	1	(0.3)	81	0		731	1	(0.1)
>5.8 mEq/L	281	3	(1.1)	81	0		731	14	(1.9)
Serum bicarbonate									
<15.1 mEq/L	283	2	(0.7)	83	0		734	0	
>34.9 mEq/L	283	1	(0.3)	83	2	(2.4)	734	2	(0.3)
Calcium									
<7.0 mEq/L	283	0		81	0		733	0	
>11.0 mEq/L	283	0		81	1	(1.2)	733	3	(0.4)
Glucose									
<45 mg/dL	282	2	(0.7)	83	0		733	4	(0.5)
>300 mg/dL	282	11	(3.9)	83	6	(7.2)	733	37	(5.0)
Blood urea nitrogen									
>35 mg/dL	283	20	(7.1)	83	9	(10.8)	730	50	(6.8)
>2.5 x ULN	283	0		83	0		730	4	(0.5)
Creatinine									
>2.0 mg/dL	283	8	(2.8)	83	3	(3.6)	733	9	(1.2)
>2.5 x ULN	283	1	(0.4)	83	0		733	4	(0.5)
Creatine kinase									
>1000 U/L	283	4	(1.4)	83	0		734	5	(0.7)

[1] Notable liver function values are presented in Section 9.9.2

[2] Number and percent of patients who developed a clinically notable value in the respective category.
Source: Modified from Tables 4.2 and 12.8.10 of Safety Update.

9.8 Antibodies to Abarelix

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.

Medical Officer's Comment

- **Although the Sponsor believes that the assay to detect IgG antibodies to abarelix has been fully validated, a positive finding (presence of antibodies to abarelix) has never been observed. Although this may be a valid finding, it is also possible that the assay does not recognize antibodies to abarelix or to abarelix-protein complexes as may exist *in vivo*. Until the Sponsor identifies antibodies to abarelix in at least one patient, the validity of the assay must remain questionable.**

9.9 Safety Issues of Special Concern

9.9.1 Allergic Reactions

9.9.1.1 Cutaneous Disorders

Allergic-type skin disorders occurring through Day 169 and reported to have an unknown, possible, probable, or definite relationship to Study Drugs are summarized in Table 39.

Table 39. 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.

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.**

9.9.1.2 Allergic Reactions for Which Patients Were Withdrawn from the Clinical Trials or Which Occurred Immediately Postdosing

A total of 20 patients participating in the abarelix clinical development program were either withdrawn because of an allergic type of reaction (n=18), experienced an immediate post-dosing hypotensive reaction (not classified as an allergic reaction by the investigator) that led to withdrawal (n=1), or experienced an immediate post dosing allergic reaction but continued treatment without further sequelae (n=1). Seventeen (17) of these 20 patients were treated with abarelix. Table 40 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.

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Table 40. 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
149-99-04	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
Abacus	THY-JP	Abarelix	Immediate	Yes
Abacus	DRO-JA	Abarelix	5 min	Yes
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	No
149-99-03	301-1295	Lupron	6 days	No
Abacus	21540077	Abarelix	1 day	No
Abacus	7450299	Goserelin	10 days	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.
Source: Tables 6-I, 6-U and pgs 105 and 114 of Safety Update, Supplemental Safety Submission of 6 April 2001, CIOMS Reports for ABACAS 1.

Fourteen (14) of the 20 reactions (all in the abarelix group) occurred within 1 hour of dosing. Thirteen (13) of these 15 reactions occurred within 15 minutes of dosing. Allergic signs or symptoms in 6 of the 20 patients included loss of consciousness and or hypotension. These latter 6 reactions all occurred in patients receiving abarelix and all occurred within 10 minutes of dosing.

Medical Officer's Comment

- **The clinical presentations of the systemic reactions in at least 15 of the 17 patients receiving abarelix are clearly different than those observed in patients receiving Lupron or goserelin. These 15 reactions occurred within 2 hours of dosing while the 3 reactions in patients receiving Lupron or goserelin occurred several days after dosing. The clinical presentation of several of the rapidly occurring reactions 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 15 patients with an early 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 41.

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Table 41. 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] NI = Not indicated;
[3] RCM = Radiocontrast media.

(continued)

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
THY-JP	Abacus 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
DRO-JA	Abacus 1	A	Felt warm with red face and chest; **Hypotension (82/50);** Generalized pruritus	15	Day 365	5 min	Clemastine IV Hospital x 24 hr		Yes
21540077	Abacus 1	A	Cutaneous erythema, itching on extremities	9	Day 229	One day after	NI	NI [3]	Yes
7450299	Abacus 1	G	Rash, pruritus on neck and ears	2	Day 29	10 days	None	NI	Yes

[1] L = leuprolide depot, A = abarelix depot, G = goserelin plus bicalutamide.
[2] Investigator called event vasovagal reaction of unknown etiology;
[3] NI = Not indicated;
[4] RCM = Radiocontrast media.
Source: Same as Table 40 above.

One reaction (Patient THY-JP) occurred immediately after the first dose of abarelix. The remaining reactions occurred after later dosings as shown below.

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	1
5	2
6 to 10	2
> 10	3

Source: See Table 41 above.

Medical Officer's Comments

- **Allergic reactions occurred throughout the treatment period ranging from immediately after first dosing to as late as Study Day 617. The wide distribution of allergic reactions relative to the onset of 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.**
- **The Sponsor did not check for the presence of IgE antibodies in patients who had immediate systemic allergic reactions nor was postdosing skin testing or other immunologic testing performed. The Sponsor did screen all patients for the development of IgG type antibodies to abarelix. None were detected. It is likely that if abarelix were sufficiently antigenic to induce the formation of IgE antibodies, it also would have induced the formation of IgG antibodies in some patients.**

9.9.1.3 Frequency of Systemic Allergic Reactions

The frequency of systemic allergic reactions that either (a) resulted in withdrawal of the patient from the clinical trial or (b) occurred within 1 hr post dosing is presented in Table 42. Seventeen (17) cases of systemic allergic reaction occurred in 1166 patients exposed to abarelix (1.5% of patients). Three (3) cases of systemic allergic reaction occurred in 457 patients exposed to Lupron or goserelin (0.7% of patients). There were 14 cases of immediate reaction (within 1 hour of dosing) in the abarelix group (1.2% of patients) and no cases of immediate reaction in the Lupron/goserelin group. Six (6) of the abarelix group experienced syncope or hypotension (0.5%). None of the patients in the Lupron/goserelin group experienced syncope or hypotension.

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Table 42. Proportion of Patients Experiencing Systemic Allergic Reactions

Treatment Group	Treated Patients N	Had Systemic Reaction n (%)	Had Immediate Reaction (<1 hr) n (%)	Had Syncope or Hypotension n (%)
Abarelix	1166	17[1] (1.5%)[2]	14[3] (1.2%)	6[4] (0.5%)
Lupron or Goserelin	457	3 (0.7)	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 1.3%.
[3] Includes patients 333-3336 and 16-3028.
[4] Includes patient 333-3336. Exclusion of this patient reduces the percentage to 0.4%
Source: See Table 41 above.

The sponsor, in the response of April 6, 2001 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/goserelin treatment groups (Table 43). The sponsor's analysis did not consider patient 333-3336 or 16-3028 as having had a systemic allergic reaction. The sponsor argued that the risk of an allergic reaction should be consider in terms of patient-years of exposure to Study Drug and not on number of patients exposed to Study Drug. The basis for this position was that the average exposure to Study Drug for the abarelix group (0.79 years/patient) was greater than that in the Lupron/goserelin group (0.60 years/patient).

Table 43. Incidence of Systemic Allergic Reactions to Abarelix (Sponsor's Analysis)

	Lupron or goserelin N = 457	Abarelix N = 1166
Number of patients withdrawn due to an allergic adverse event	3	15
Proportion of patients withdrawn due to an allergic adverse event	0.66%	1.29%
Average years of exposure to Study Drug per patient	0.60 years	0.79 years
Number of patients withdrawn due to an allergic event per 100 years of exposure	1.1 pts	1.63 pts

Source: Supplemental Safety Submission of 6 April 2001.

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, the ratio of 1.63/1.1 is not significantly different than the ratio of 1.29/0.66. Most importantly, since no patients in the Lupron/goserelin groups experienced an allergic reaction that occurred within 1 hours of dosing or that involved loss of consciousness or hypotension, the manner by which the relative risk is calculated (simple proportions or patients years of exposure) is not important.**

9.9.1.4 Medical Officer's Recommendations and Assessment of Relative Risk Associated with Allergic Reactions during Treatment with Abarelix

- **The Sponsor will be asked to obtain further information about the mechanism(s) responsible for the immediate allergic reactions. Procedures that would be helpful include screening of sera for IgE antibodies and intradermal skin testing. The sponsor should screen for allergic sensitivity to carboxymethylcellulose (previously reported to cause anaphylactic reactions) as well as abarelix by intradermal testing.**
- **The pathophysiological mechanism(s) responsible for these systemic and serious allergic reactions is not known and may be anaphylactoid, anaphylactic, or both in etiology. Because of the well known propensity of GnRH antagonists to directly release histamine**

from mast cells (similar to that observed with opioids), a direct pharmacological effect of abarelix should not be excluded at this time.

- **The reported severity and incidence of these systemic allergic reactions in this NDA application and the limited number of patients who would derive significant benefit from avoidance of a testosterone surge and the accompanying symptoms of flare raise concerns about the risk-benefit ratio for abarelix (see Section 12.1).**
- **Although no patients have died or have been reported to suffer any sequelae from these systemic reactions, they represent a serious safety concern. Before abarelix could be approved for marketing, the sponsor will need to (1) conduct additional clinical investigations to elucidate the mechanism(s) responsible for the reported serious anaphylactic-like reactions, (2) reduce the incidence of these reactions or make all reasonable efforts to reduce their incidence, and (3) develop risk management procedures and education programs for medical care providers and patients to maximize the safe use of abarelix.**

9.9.2 Hepatic Toxicity

Medical Officer's Comment

In Phase I/II 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 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 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 principal safety studies.

9.9.2.1 Liver Function Test Values (Changes from Baseline)

Mean and median values for liver function tests and absolute changes from baseline were reviewed for the principal 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 44).

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 44. 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	Lupron +Casodex	Abarelix
	(N = 284)	(N= 83)	(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.

9.9.2.2 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 45) and the uncontrolled studies (Table 47). Pooled results for the controlled studies are presented in Table 46. 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 46 includes pooled data from the controlled studies. The comparisons presented in Table 46 include pooled data from Lupron-treated patients (Column 1, Studies 149-98-02 and 149-99-03), pooled data from Lupron or Lupron plus Casodex treated patients (Column 3, Studies 149-98-02, 149-98-03, and 149-99-03) as well as pooled data from abarelix-treated patients from all controlled studies (Column 4). Data in Table 46 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. However, the percentages of patients with shifts to high (> ULN) for bilirubin in the abarelix group are comparable to those in the Lupron groups.

In the uncontrolled studies (Table 47), 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 48 (all 3 controlled studies for the interval Days 1-169 and Days 1-365 presented separately) and in Table 49 (includes data only from Studies 149-98-02 and 149-98-03) and for AST in Table 50. 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, and Grade 3 toxicity, respectively, during Study Days 1-169 (Table 48, upper panel). Changes of similar magnitude were observed for ALT values in the abarelix group for the period Days 1-365 and for pooled data from Studies 149-98-02 and 149-98-03.

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 (above the 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 45).**

Table 45. 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 postbaseline 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.

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Table 46. Liver Function Test Shifts to High (>ULN) in Controlled Studies (Studies 149-98-02, 149-98-03, 149-99-03, Combined Analysis).

Laboratory Test	Lupron N = 284		(Lupron+Casodex) N = 83		Lupron plus (Lupron+Casodex)[A] N = 367		Abarelix Depot N = 735	
	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] Includes patients who received Lupron in Study 149-98-02 and Lupron plus Casodex in Study 149-98-03.
[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.

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Table 47. 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	3 (25)	259	29 (11)
ALT	12	1 (0)	256	35 (14)
AST	13	2 (15)	262	37 (14)
Total bilirubin [6]	13	1 (8)	273	2 (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 postbaseline value.
[5] Patients whose baseline value on Study 149-99-04 was not high and who had a least 1 postbaseline 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; and Table 12.6.4 of Safety Update.

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Table 48. 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 49. ALT Shift in Toxicity Grade - Baseline to Most Extreme On-Study Value through Day 365 (Pooled Data from Controlled Studies 149-98-02 and 149-98-03)

		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	0	0	0	0	0	0	0	1	0	0	0	0	0
	0	65 (74)	0	0	0	0	65	72 (87)	0	0	0	0	72	240 (69)	2 (1)	0	0	0	242
	1	17 (19)	2 (2)	0	0	0	19	9 (11)	0	0	0	0	9	81 (23)	2 (1)	1 (<1)	0	0	84
	2	1 (1)	3 (3)	0	0	0	14	1 (1)	0	0	0	0	1	12 (3)	4 (1)	0	0	0	16
	3	1 (1)	0	0	0	0	1	1 (1)	0	0	0	0	1	5 (1)	0	0	0	0	5
	4	0	0	0	0	0	0	0	0	0	0	0	0	1 (<1)	0	0	0	0	1
	Total	84	5	0	0	0	89	83	0	0	0	0	83	339	8	1	0	0	348

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 4.1.3, pg 192, Safety Update. Percentages calculated by medical reviewer.

Table 50. 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

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.

9.9.2.3 Clinically Notable Liver Function Test Values

Clinically notable liver function test values are listed by study for the controlled studies (Table 51) and the uncontrolled studies (Table 53). Pooled results for the controlled studies are presented in Table 52. 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 51).

Data for the controlled studies also were pooled across studies in a manner similar to that described previously in Section 9.9.2.2. In the combined comparisons for the controlled studies (Table 52), there was a numerically higher (albeit small) percentage of patients in the abarelix group, compared to the Lupron 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 group, 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).**
- **The high proportion of patients with clinically notable alkaline phosphatase values in Study 149-98-04 is most likely a consequence of the patient's advanced state of prostate cancer and the higher incidence of bone metastases in such a population.**

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Table 51. 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 postbaseline 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.

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 postbaseline 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..

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.

Table 52. Clinically Notable Liver Function Test Values (Pooled Studies 149-98-02, 149-98-03, 149-99-03)

	Treatment Group											
	Lupron (N=284)			Lupron + Casodex (N=83)			Lupron (N=284) + [Lupron + Casodex] (N=83)			Abarelix (N=735)		
Laboratory Test	Eval[1]	Experienced[2]		Eval	Experienced		Eval	Experienced		Eval	Experienced	
	n	n	(%)	n	n	(%)	n	n	(%)	n	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)

[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 51 on pg 100 of this review (Calculated by medical reviewer).

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Table 53. 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[1] 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.

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 1 of 149-98-04 Study Report.

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[1] n	Abarelix Depot 100 mg (N = 278) Experienced n (%)
Alkaline phosphatase	> 200 U/L	14	0	275	5 (2)
	> 5.0 x ULN	14		275	1 (1)
ALT	> 2.5 x ULN	14	0	275	5 (2)[2]
	> 200 U/L	14		275	1 (<1)[2]
AST	> 2.5 x ULN	14	0	275	5 (2)[2]
	> 200 U/L	14		275	1 (<1)[2]
Total bilirubin	> 2.5 x ULN	14	0	275	0

[1] Patients whose baseline value on Study 149-99-04 was not in the clinically notable range or whose postbaseline value was worse than their clinically notable baseline value.
[2] Patient 338-2164 withdrew from the study per protocol; subsequent decrease in transaminases.
Source: Table 12.6.7 (Section 12) of Safety Update.

9.9.2.4 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 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 initially observed elevation.

Four patients in the abarelix depot group and 2 patients in the Lupron plus Casodex group developed transaminase elevations that required withdrawal in accordance with the study protocols (Table 54). No patients receiving Lupron 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 54. 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 who were treated with Lupron alone was terminated because of elevated 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) had a single elevated bilirubin value (see Table 54).**

- **Although abarelix appears to have greater hepatotoxicity than Lupron, no patient under the conditions of the controlled clinical trials experienced serious or irreversible liver damage as assessed by serum bilirubin levels.**
- **Transaminase levels in the controlled clinical trials were monitored monthly or more frequently. It is not know if patients that were withdrawn for elevated transaminases would have progressed to more serious, perhaps irreversible, stages of liver damage if they had not been monitored monthly.**
- **The adverse effects of abarelix on the liver appear to be a manageable risk that will be addressed in labeling and will require the monitoring of serum transaminase levels.**

9.10 Safety Consults

The Division of Pulmonary and Allergy Drug Products (DPADP) was consulted regarding the issue of systemic allergic reactions that occurred almost immediately after dosing with abarelix in some patients. The consultants stated in their review that "the allergic reactions seen in the abarelix-treated patients were consistent with the spectrum of symptoms and signs of systemic allergic reactions, including anaphylaxis." They identified 6 patients who they believed had shown signs and symptoms of anaphylaxis with hypotension or syncope among 1166 patients who had been treated with abarelix. They identified no cases of anaphylaxis in 367 patients treated with Lupron, Lupron plus Casodex, or goserelin. The consultants felt that the allergic reactions were most likely IgE mediated (anaphylactic) but also be could be a result of a direct action of abarelix on mast cells and basophils causing the release of histamine from these cells. In their opinion, these reactions represented a significant safety concern and would need to be carefully considered in arriving at a final regulatory decision regarding the approvability of abarelix. They recommended that the Sponsor conduct additional investigations, including appropriate intradermal testing and screening for the presence of IgE antibodies, to better understand the mechanism(s) responsible for these systemic allergic reactions.

9.11 Adequacy of Patient Exposure and Safety Assessment

A total of 1079 prostate cancer patients were exposed to abarelix depot in studies sponsored by Praecis. An additional 87 prostate cancer patients received the proposed 100 mg registration dose of abarelix in Study ABACUS 1 (sponsored by Sanofi-Synthelabo). Of the 1079 patients in Praecis sponsored studies, 834 patients received the proposed registration dose of abarelix (100 mg for both induction [initial 1 or 2 doses] and maintenance of medical castration). A total of 752 of these patients were exposed to the proposed registration dose of abarelix for at least 6 months, and 190 patients were exposed for at least 1 year.

Medical Officer's Comments

The size of the clinical program was relatively small for a new molecular entity. It was adequate, however, to assess the likely safety of abarelix in the intended population (i.e., elderly men with advanced carcinoma of the prostate). Protocol-designated safety assessments (both clinical and laboratory) were performed monthly or more frequently in the 3 controlled safety studies. The safety assessments were appropriate and adequate with one exception. The exception was that the Sponsor did not investigate further or follow up patients who experienced immediate postdosing systemic reactions to abarelix. These patients should have undergone at a minimum (1) intradermal testing with abarelix decapeptide, abarelix depot. and carboxymethylcellulose (CMC) and (2) screening of their serum for the presence of IgE antibodies to abarelix or CMC. Neither of these procedures was conducted. Consequently, there is presently inadequate information about the underlying pathophysiology of these serious systemic reactions.

9.12 Safety Findings and Proposed Labeling

Two safety concerns were identified during the review of this NDA: (1) systemic allergic reactions, some of which were associated with hypotension and loss of consciousness immediately after dosing (i.e., anaphylactic-like reactions that occurred in 0.4%-0.5% of abarelix-treated patients), and (2) increases in hepatic transaminases that were reversible either during continued dosing (generally mild elevations) or upon discontinuation of treatment with abarelix. Both of these safety issues are referred to in the proposed label. However, the possibility of a patient experiencing a serious systemic reaction has not been sufficiently stressed in labeling. This risk will require that a boxed warning be added to the label. In addition, a statement that patients must be observed for 1 hour after dosing and that physicians be prepared to treat a serious anaphylactic reaction should it occur (i.e., have the necessary medications and medical expertise) should be added. More specific guidance to the physician regarding monitoring for possible hepatotoxicity also needs to be provided in labeling.

10 USE IN SPECIAL POPULATIONS

Abarelix is to be used only for the management of advanced prostate cancer. This will limit its target population primarily to elderly men. It is not intended to be used in women or children for the indication that is under review. Abarelix has not been studied in children [redacted]. Based on the present safety profile of abarelix, it should be labeled to clearly exclude its use in any group other than men with far advanced prostate cancer.

The pharmacokinetics of abarelix was not evaluated in renally or hepatically impaired patients.

The sponsor performed standard subset safety 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). No obvious differences across these groups were identified. However, the total number of African American patients included in these analyses was small (n = 71) and only 152 patients were less than 65 years of age.

11 PACKAGE INSERT

The proposed package insert is not reviewed in detail in this document as the label will need to be extensively revised, based on presently available safety data and to-be-obtained new safety data concerning the pathophysiology of the immediate postdosing systemic allergic reactions that have been observed. The need for a revision of the section on claimed efficacy, betters guidance to the physician for the monitoring of serum testosterone (an efficacy concern) and liver transaminase levels, and appropriate warnings (including a boxed warning) regarding the risk of anaphylactic reactions have been addressed elsewhere in this review.

The Sponsor's proposed indication is too broad. Until further information about the cause of the serious, immediate postdosing systemic reactions is obtained and the risk of these reactions is substantially reduced (i.e., less than 0.1%), the use of abarelix must be restricted to men with advanced prostate cancer who may experience serious injury (e.g., spinal cord compression) were they to be treated with a superactive GnRH agonist such as Lupron.

12 CONCLUSIONS AND RECOMMENDATIONS

12.1 Overall Risk-Benefit Analysis

12.1.1 Benefits of Treatment with Abarelix Compared to Other Medical Options

No hormonal therapy for the management of advanced prostate cancer is more effective than orchiectomy. Superactive agonists of GnRH, such as Lupron, that suppress serum testosterone to castrate levels (i.e., ≤ 50 ng/dL) have been shown to have comparable long-term efficacy as orchiectomy as assessed by time to disease progression and survival. Achievement of castrate levels

of serum testosterone is generally obtained by 1 month after the start of therapy with a GnRH superactive agonist. In contrast to surgical castration, however, treatment with a GnRH agonist initially results in a significant, albeit temporary (~1 to 2 weeks), increase in gonadal androgen production and secretion. The initial rise in serum testosterone may cause a temporary worsening of symptoms, "a flare." Most commonly, the immediate consequence of this initial increase in circulating androgen levels is an increase in bone pain in those patients with bone metastases. Less frequently, more serious adverse events can occur, including ureteral obstruction, bladder neck outlet obstruction, spinal cord compression and paralysis, and rarely, death. The long-term consequences of the initial transient increase in testosterone secretion on disease progression, if any, are not known.

For these reasons, superactive GnRH agonists must be used with caution in patients presenting with large local lesions and are generally considered inappropriate therapy, unless administered with concomitant antiandrogen therapy (e.g., Casodex), for men with vertebral metastases or neurologic symptoms of spinal cord compression. Antiandrogens, however, have their own spectrum of adverse effects, and it has not been shown that they completely block the adverse consequences of an androgen surge, particularly in the presence vertebral metastases or impending spinal cord compression.

Short term or early benefits of abarelix. Abarelix, in contrast to superactive GnRH agonists, is a true GnRH antagonist that is devoid of LH and FSH releasing activity. Consequently, abarelix should be able to more rapidity reduce serum testosterone to castrate levels without an initial antecedent surge. In the controlled clinical trials presented in this NDA, no patients in the abarelix treatment groups experienced a testosterone surge (defined as an increase in testosterone of > 10% above baseline values). In contrast, 82% (Study 149-98-02) and 86% (Study 149-98-03) of patients in the active control groups experienced a surge of testosterone ($p < 0.001$). In the controlled clinical trials with abarelix, the endpoint for rapidity of medical castration was defined as a serum testosterone value $\leq$ 50 ng/dL on Study Day 8. No patients in the active control groups were medically castrate on Day 8 compared with 72% and 68% of the patients in the abarelix group in Studies 149-98-02 and 149-98-03, respectively ($p < 0.001$). In summary, the sponsor has demonstrated with high statistical probability that treatment with abarelix suppresses serum testosterone levels more rapidity than does treatment with Lupron (a superactive GnRH agonist) and does so without initially producing a testosterone surge.

Both of these aspects of treatment with abarelix are of clinical benefit, particularly the absence of a surge in certain high risk patients such as the 81 patients with advanced prostate cancer that were treated with abarelix in Study 149-98-04. These patients, for the most part, had symptoms or physical findings that strongly suggested that treatment with a superactive GnRH agonist, without concomitant antiandrogen therapy, might result in a clinically significant exacerbation of their symptoms or a medically serious complication. Entry criteria for this Study required that patients have 1 of the following 4 conditions: bone pain from skeletal metastases, bilateral retroperitoneal adenopathy causing ureteral obstruction, impending neurological compromise, or the presence of an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction. Serum testosterone was reduced to $\leq$ 50 ng/dL in 30% and 79% of patients in Study 149-98-04 on Study Days 2 and 8, respectively. All of these patients avoided orchiectomy, demonstrating that abarelix could be administered to these high risk patients without a serious exacerbation in their symptoms of prostate cancer. It is not known, however, what percentage of these patients would have had a testosterone surge of sufficient magnitude to necessitate an orchiectomy had they been treated with a superactive GnRH agonist and an antiandrogen.

Absence of long term benefits. Reliable long term suppression of testosterone to castrate levels is an essential component of the hormonal management of advanced prostate cancer. For most patients, the adverse consequences of inadequate and/or unreliable long term suppression of testosterone are likely to be of greater importance than an initial increase in serum testosterone levels of 1 to 2 weeks

duration. In the present NDA, the Sponsor has demonstrated that the capacity of abarelix to maintain castrate levels of testosterone was not inferior that of Lupron or Lupron plus Casodex through the first 85 days of therapy. When the observation period for efficacy was extended to 169 days (not a requirement of the agreed upon primary endpoint), abarelix did not quite meet the criteria for non-inferiority in 1 of the 2 primary efficacy studies as the lower bound of the 95% CI for the difference in maintenance of testosterone suppression slightly exceeded the agreed upon lower limit of –10% (95% CI was [-12.3, 2.5] in Study 149-98-02). When more rigorous definitions for maintenance of testosterone suppression were used as discussed in Section 8.4.3.2, abarelix was not non-inferior, and was possibly inferior, to Lupron in one of the 2 principal efficacy studies (Study 149-98-02, 95% CI:-21.0, -0.9).

Summary. Abarelix appears to provide some potential clinical benefits (not rigorously proven) over a superactive GnRH agonist for the initial hormonal management of some men with advanced prostate cancer, particularly those with impending spinal cord compression or ureteral obstruction secondary to vertebral or retroperitoneal metastases, respectively. However, [redacted] abarelix does not provide any benefits over those of a superactive GnRH agonist and is likely to be somewhat inferior (at least to Lupron) when administered once monthly in accordance with the proposed dosing regimen.

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

During clinical trials with abarelix, 2 safety concerns were identified: hepatic toxicity and serious systemic allergic reactions.

Hepatic toxicity. A greater proportion of patients treated abarelix in the controlled safety trials had an increase in serum transaminase levels (particularly ALT levels) than patients treated with Lupron alone or Lupron plus Casodex. These increases were, for the most part, completely reversible, either with continued dosing (generally with mild elevations) or following discontinuation of treatment (with more significant elevations). None of the increases was associated with clinical jaundice and none (with one exception) was associated with an increase in bilirubin to > 2.5 x ULN. (The exception was a patient whose bilirubin increase was attributed to pancreatic cancer). The adverse effects of abarelix on the liver appear to be a manageable risk that can be addressed in labeling and will require the monitoring of serum transaminase levels.

Allergic reactions. Allergic reactions that were observed in patients treated with abarelix included those limited to cutaneous manifestations and those with serious systemic, immediate adverse manifestations (decrease in blood pressure and/or loss of consciousness). Delayed cutaneous reactions occurred in a similar proportion of patients in both the abarelix and active control treated patients. Immediate systemic reactions (occurring within 1 hour of dosing) were observed only in the abarelix groups and were reported for 14 of 1166 patients (1.2%). Immediate systemic reactions that were associated with hypotension and/or loss of consciousness were reported in 5 or 6 of 1166 (0.4%-0.5%) patients treated with abarelix. All of these patients recovered rapidly with medical intervention and without any known sequelae.

Although no similar reactions were observed in the Lupron treated patients, serious anaphylactic reactions have been reported in patients receiving Lupron and other superactive GnRH agonists. The incidence of such reactions is not known, but they appear to occur with a frequency well below that observed in the abarelix-treated patients. A review of the FDA post marketing adverse event reporting system database identified only 23 cases of anaphylaxis in Lupron treated patients. Lupron was first approved for the treatment of prostate carcinoma in 1985 and for the treatment of endometriosis in 1989. It is the most widely used superactive GnRH analog in the US for treatment of these disorders. The current package insert for Lupron states that "symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported with an incidence of 0.002%."

12.1.3 Summary of Risk-Benefit Analysis

Abarelix, a true GnRH antagonist, appears to offer a clinical benefit over Lupron and other superactive GnRH agonists for the hormonal treatment of some men with advanced prostate cancer. Such men are those with metastatic lesions in critical locations (i.e., adjacent to the spinal cord or ureters) that are likely to expand and produce serious clinical sequelae in response to the initial surge of testosterone that occurs following treatment with a superactive GnRH agonist. The number of such men, however, represents a decreasing percentage of men who are newly diagnosed with prostate cancer as diagnostic procedures for early detection continue to improve. Abarelix offers no proven benefit over conventional GnRH agonist therapy for other men with prostate cancer. In its present formulation and with the Sponsor's recommended dosing regimen, it is likely to be somewhat less effective than once-monthly Lupron in reliably suppressing serum testosterone to levels $\leq$ 50 ng/dL during long term treatment. Because of the risk of a serious systemic reaction in 0.4%-0.5% of patients, the present risk-benefit ratio for abarelix does not warranted its use for the treatment of prostate cancer in most men. Approval for use in those patients at high risk for developing a serious complication following initiation of treatment with a superactive GnRH agonist may be warranted after (1) the Sponsor conducts additional investigations to elucidate the mechanism(s) responsible for the immediate postdosing serious systemic reactions (2) and is able to reduce, or has made all reasonable efforts to reduce, the incidence of these reactions.

12.2 Major Issues with Regard to Sponsor's Proposed Package Insert

These issues are discussed in Section 11 of this review.

12.3 Approvability

12.3.1 General Recommendation

It is recommended that abarelix suspension (NDA 21-320) receive an approvable action. Based on the demonstrated safety profile of abarelix and the incidence (0.4-0.5%) of serious, anaphylactic-like reactions observed in clinical trials to date and the available alternative of orchiectomy for therapy in higher risk patients, approval cannot be recommended at this time. The use of abarelix (when and if approved) should be limited to men with advanced prostate cancer in whom (1) orchiectomy is not an acceptable treatment option and (2) treatment with a superactive GnRH agonist, such as leuprolide or goserelin, is likely to produce a serious exacerbation of the patient's disease. Such patients would include men with metastatic lesions adjacent to the spinal cord and those with partial ureteral obstruction due to their prostate cancer.

12.3.2 Specific Recommendations

Prior to approval of abarelix for use in the limited population described in Section 12.3.1, the sponsor will need to:

1. Conduct additional clinical investigations to elucidate the mechanism(s) responsible for the reported serious anaphylactic-like reactions.
2. Reduce the incidence of these reactions based on information obtained from Item No. 1 above or make all reasonable efforts to reduce their incidence.
3. Agree to implement risk management procedures and education programs for medical care providers and patients to ensure that:
   a) The use of abarelix is limited to the high risk population described above.
   b) Physicians and patients are informed of the additional risk associated with the use of abarelix, namely, potentially life-threatening anaphylactic-like reactions.
   c) Physicians are prepared to treat an anaphylactic-like reaction should it occur.

d) Patients are observed for 1 hour after each dosing.

4. Provide appropriate drug labeling regarding

   a) The occurrence of anaphylactic or anaphylactoid reactions in 0.4-0.5% of patients treated with abarelix in clinical trials. Labeling will require a boxed warning concerning this risk.

   b) The possibility of hepatotoxicity and the need for monitoring of serum transaminase levels.

   c) The possibility that up to 20% of patients treated with abarelix may not maintain serum testosterone levels ≤ 50 ng/dL when treated for up to 1 year.

   d) Provide guidance for appropriate monitoring of serum testosterone levels to identify patients with inadequate suppression.

5. Commit to conducting Phase IV dose optimization studies to reduce the proportion of subjects who do not have adequate long-term suppression of serum testosterone. Such studies might investigate (a) a shorter interval between each dosing with abarelix, (b) a modification of the formulation to delay the early release of abarelix, and (c) increasing the dose or dosing frequency of abarelix for men who weigh more than 200 pounds.

In regard to the most important of these recommendations (Items 1-3 above), the sponsor should conduct additional follow up investigations for those patients who previously had an immediate post dosing reaction. Such testing should include (1) screening for the presence of IgE antibodies to abarelix (free peptide), the abarelix-carboxymethylcellulose complex (abarelix-CMC), and free CMC, and (2) appropriate intradermal testing with abarelix (the free peptide), abarelix-CMC, and free CMC, both in patients who had an immediate reaction and a control group of abarelix-treated patients who did not exhibit such reactions. In addition, since these reactions may be a consequence of a direct non-immunologic effect of abarelix (an anaphylactoid reaction), measurements of abarelix serum levels in samples obtained at the time of or immediately after the systemic reactions would be of value. Depending on the findings from these investigations, the sponsor may be able to change the formulation of abarelix (e.g., elimination of CMC or change the early release profile of abarelix) and thereby reduce the incidence of these systemic reactions.

/S/

Scott E. Monroe MD

Medical Officer, DRUDP

Date

NDA 21-320
Plenaxis™ (abarelix for injectable suspension)
Praecis Pharmaceuticals, Inc.

Medical Officer Review for Clinical Trial 149-98-04.

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/s/

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Executive Summary for **Clinical Trial 149-98-04** ("A Multi-Center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contradicated")

Materials reviewed: The following materials were reviewed: 1) interim and final study reports for Trial 149-98-04 2) selected portions of the integrated summary of safety and 3) two standard urology textbooks and 42 journal articles dealing with clinical "flare" following LHRH administration.

Recommendation: This reviewer believes that Trial 149-98-04 supports the approval of abarelix for limited use only in those patients with far advanced prostate cancer (not currently on hormonal therapy) who are at significant risk for clinical "flare" secondary to testosterone "surge." These patients would include those with impending spinal cord compression, azotemia secondary to hydronephrosis, impending urinary retention, and impending long bone or spine fracture. A boxed warning concerning anaphylactic/anaphylactoid reactions should be included in the label and patients should be observed for 1 hour after injection. A phase 4 commitment to better elucidate the mechanism(s) of allergic reactions should be required.

Introduction: Current therapy of advanced prostate cancer is primarily hormonal (orchiectomy versus LHRH agonist) and therapy is directed at reducing serum testosterone (T) to castrate levels (<50 ng/dL). Orchiectomy results in a decrease in serum testosterone levels to castrate levels in approximately 4 to 8 hours. LHRH agonists cause an initial testosterone "surge" in >80% of patients because of initial stimulation of LH release. Testosterone levels are increased 50 to 100% for approximately 2 weeks. Testosterone levels then fall and castrate levels of T are achieved by approximately 95% of patients by 28 days. This testosterone "surge" has been associated with clinical "flare" in 5 to 10% of patients treated with LHRH agonists. A potential advantage of abarelix (a GnRH antagonist) is the lack of testosterone "surge" and, therefore, absence of clinical "flare." Trial 149-98-04 was designed to investigate abarelix in a group of patients who were considered at high risk for clinical "flare" and in whom LHRH agonists are "contraindicated."

Design and conduct summary: Eighty-three patients in whom LHRH agonists were "contraindicated" were enrolled in this open-label, multi-center (18 US and 1 Mexico) trial. All patients had 1 of the 4 following conditions secondary to prostate cancer: 1) bone pain from skeletal metastases 2) bilateral retroperitoneal adenopathy causing ureteral obstruction 3) impending neurological compromise and/or 4) the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction. Patients received 7 doses of abarelix depot 100 mg on Days 1, 15, 29, 57, 85, 113, and 141.

Reviewer's comment: LHRH agonists are not "contraindicated" in the 4 conditions listed. Because of the testosterone "surge" seen with LHRH agonists, product labels describe clinical "flare" in the warnings section and state that patients with any of the 4 conditions listed should be "closely observed" during LHRH therapy.

Efficacy summary: The primary efficacy endpoint was the avoidance of orchiectomy at Days 29 and 85. These results are shown in Table 1.

Table1. Percentage of patients who avoided orchiectomy through day 29 and through day 85 (N=72).

	Avoided orchiectomy N (%)	95% confidence interval
Through day 29	70 (97%)	(90.3, 99.7)
Through day 85	70 (97%)	(90.3, 99.7)

Two patients who withdrew for treatment related adverse events (patient 416-4067 on day 15 for urticaria and patient 409-4057 on day 29 for allergic reaction) were considered failures to avoid orchiectomy on days 29 and 85 as specified in the statistical analysis plan although neither actually underwent orchiectomy. Five other patients withdrew from the study after day 29 and before day 85 (2 patients died of prostate cancer, 1 patient withdrew voluntarily, 1 patient was withdrawn by the investigator because the patient's veins were not accessible, and 1 patient was withdrawn by the investigator because he did not meet the inclusion criteria). Since none of these 5 patients were withdrawn from the study because of a treatment related adverse event, all 5 patients were considered to have avoided orchiectomy based on LOCF as defined in the statistical analysis plan.

Secondary endpoints included the percentage of patients who achieved castrate levels of serum T by visit day. These results are shown in Table 2.

Table 2. Percentage of patients with T levels < 50 ng/dL by visit day (N=72)

	Evaluated (N)	Castrate (N,%)
Baseline	72	2 (3%)
Day 2	67	20 (30%)
Day 8	72	57 (79%)
Day 15	72	63 (88%)
Day 29	71	68 (96%)
Day 85	65	63 (97%)
Day 169	59	55 (93%)

None of the patients experienced a testosterone "surge" at any time point.

Reviewer's comment: This trial was not designed to evaluate the ability of abarelix to maintain castrate levels of testosterone for periods longer than 169 days.

Safety summary: None of the patients experienced disease exacerbation or clinical "flare" following injection of abarelix depot.

The symptomatic condition allowing study entry is shown in Table 3.

Table 3. Symptomatic condition for study entry (N=72)

Condition for study entry	N (%)

Impending neurological compromise	6 (8%)
Ureteral obstruction	9 (13%)
Enlarged prostate or pelvic mass	25 (35%)
Bone pain from skeletal metastases	31 (43%)
Other	1 (1%)

Impending neurologic compromise group: No exacerbation of impending neurologic compromise or overt neurologic signs or symptoms developed in these 6 patients following the administration of abarelix.

Reviewer's comments: It is not clear whether these 6 patients had vertebral or epidural metastases. In patients with impending neurologic compromise, no neurologic symptoms and a normal neurologic examination, abarelix has potential advantages over LHRH agonist therapy because no testosterone "surge" is seen and serum T levels decrease more rapidly following abarelix-depot than after LHRH agonist therapy. The reviewer is aware of no clinical data which compare GnRH antagonists with the combination of a LHRH agonist and an androgen receptor blocking agent. In patients with acute neurologic deficits (eg paraplegia), the reviewer believes that abarelix-depot would not be appropriate as monotherapy. The use of abarelix-depot would not be expected to be as efficacious as orchiectomy because only 30% of patients receiving abarelix-depot achieved castrate levels of testosterone by Day 2.

Bilateral retroperitoneal adenopathy causing ureteral obstruction:

Reviewer's comments: It is difficult to determine whether the hydronephrosis in these patients is secondary to retroperitoneal adenopathy, locally invasive prostate cancer, or bladder outlet obstruction. In addition, 8 of the 9 patients had normal or mildly elevated serum creatinine levels (the other patient had a creatinine of 4.9 and bilateral ureteral stents in place). In patients with retroperitoneal adenopathy and a normal serum creatinine (particularly in the presence of unilateral hydronephrosis), the reviewer believes that LHRH agonist therapy is not "contraindicated."

Enlarged prostate or pelvic mass:

Reviewer's comments: Ten of the 25 patients with an "enlarged prostate or pelvic mass" had a urethral or suprapubic catheter in place at baseline. These patients exhibited no contraindication to LHRH agonist therapy. In 8 of the 10 patients, the catheter was removed during the trial (3 by Day 29, 4 by Day 85, and 1 by Day 169). No patient experienced urinary retention as a result of abarelix-depot therapy. It is not clear how many of the other 15 patients would have experienced urinary retention if they would have been treated with LHRH agonist therapy.

Bone pain from skeletal metastases:

Reviewer's comments: The investigator judged that the risk of pathologic fracture was present in 12 of the 31 patients. In patients at risk for fracture (particularly in the spine,

hip, and femur), avoiding a testosterone "surge" by treatment with abarelix-depot has potential advantages over treatment with a LHRH agonist alone. This trial was not designed to compare efficacy and safety of GnRH antagonists and LHRH agonists with or without androgen blockade.

Allergic reactions: One patient experienced a severe systemic allergic reaction (loss of consciousness, generalized skin rash, hypotension (blood pressure of 80 mmHg measured by Doppler), and peri-orbital, facial, and peripheral edema) and 2 other patients withdrew from the study because of allergic symptoms (both had urticaria). No deaths from allergic reactions occurred. The incidence of study withdrawal because of an allergic adverse event was 4%.

Reviewer's comments: The occurrence of allergic reactions (particularly severe, systemic allergic reactions) is concerning. In the combined trials submitted in this NDA, the incidence of anaphylactic/anaphylactoid reactions is 0.5%. No deaths from allergic reaction occurred in these patients. In the opinion of this reviewer, this incidence is not acceptable for the general prostate cancer population, but is acceptable in a group of patients with advanced prostate cancer who may otherwise require bilateral orchiectomy. Abarelix therapy results in castrate levels of serum T in 79% of patients at day 8 and in 88% of patients at day 15 while LHRH agonist therapy (with or without the addition of non-steroidal anti-androgen) does not result in castrate T levels until 3-4 weeks following injection. Patients need to be observed for acute allergic reactions following injection.

Elevated transaminases: Three patients experienced elevated AST and ALT to >2.5 times the upper limit of normal.

Reviewer's comment: The significance of the elevated transaminases is difficult to determine in this group of patients with advanced prostate cancer.

Importance and treatment of clinical "flare" which occurs in patients with prostate cancer treated with LHRH agonists:

In an attempt to characterize the significance and current treatment strategies of clinical flare associated with LHRH agonist administration, the reviewer consulted 2 major urology textbooks and 42 journal articles dealing with the subject. Many of the articles contained reviews or case reports, and few controlled series were identified.

It is estimated that 5-10% of patients with prostate cancer will experience clinical "flare" following the initiation of LHRH agonist therapy. Most of these "flare" episodes are manifested as an increase in bone pain, but neurologic symptoms including paraplegia, ureteral obstruction, bladder outlet obstruction, lymphedema, and sudden death have been reported. Although 3-7% of men with prostate cancer will develop neurologic problems, spinal cord compression is the presenting symptom in only approximately 1% of patients (Rosenthal, Br J Urol, 1992). In a review of 765 patients in 9 series, Thompson found a 10.9% incidence of disease "flare" and 15 (2%) of the 765 patients died during the "flare"

(Thompson, J Urol 1990). The authors conclude that "these data suggest that any patient placed on LHRH agonist therapy for prostate cancer merits some form of flare blockade during the first 1-2 months of therapy." Maher (Maher, Cancer, 1993) estimated the incidence of "flare" to be 4-33%. "This variance is due mainly to the confusion about the definition of the flare phenomenon. Many papers do not distinguish between testosterone "surge" and clinical "flare." This author concludes that "flare prevention should be initiated whenever therapy with LHRH analogues alone is prescribed." Furthermore, "it seems mandatory that flare prevention should be carried out whenever LHRH analogues are prescribed in monotherapy." The incidence of clinical "flare" is such that the recommendation has been made that "a pure or steroidal anti-androgen should be given before or at the time of initiation of LHRH agonists, especially in patients with large tumor mass." (Campbell's Urology, 1998)

Many authors believe that clinical "flare" can be completely prevented. "Biochemical and clinical "flare" can be prevented by the use of a pure or steroidal anti-androgen given either one week before the initiation of LHRH analogue or simultaneously with the initiation of LHRH treatment (Campbell's Urology, 1998). DES, cyproterone acetate, and non-steroidal anti-androgens have all been used for this purpose. In a study involving 70 patients and a total experience of 700 patients, Labrie concluded that the addition of flutamide (250 mg tid starting 24 hours prior to LHRH agonist injection) "completely eliminates the risk of disease flare" (Labrie, J Urol, 1987). Furthermore, "impending cord compression may be avoided with low dose DES or flutamide for 3 to 4 weeks before and 1 month following LHRH agonist therapy" (Adult and Pediatric Urology (Gillenwater), 1996). Finally, Brogdan believes that "while there seems little doubt that combination therapy prevents disease flare induced by the LHRH analogue alone,...(Brogdan, Drugs and Aging, 1991).

Other data indicate that anti-androgens alleviate but do not completely prevent clinical flare. Crawford treated 603 patients with leuprolide (300 treated with leuprolide alone and 303 treated with leuprolide plus flutamide). At 1 week, increased pain occurred in 23 patients in the leuprolide alone group versus 11 in the leuprolide plus flutamide group ($p<0.019$). At week 4, 33 patients were worse in the leuprolide alone group versus 20 in the leuprolide plus flutamide group ($p<0.13$). Acid phosphatase was elevated in 9 in the leuprolide alone group and in 6 in the leuprolide plus flutamide group (Crawford, NEJM, 1989). Similar results were reported by Kuhn. Thirty-six patients (17 buserelin plus nilutamide 300 mg/day and 19 buserelin plus placebo) were treated. Bone pain appeared or worsened in 5/17 buserelin plus nilutamide patients and in 12/19 buserelin plus placebo patients ($p<0.05$). Acute retention occurred in 1 patient in the buserelin alone group (Kuhn, NEJM, 1989). These data indicate that anti-androgens ameliorate but do not prevent flare. Chrisp concluded that "adding anti-androgen appears to alleviate the symptoms of flare to some extent" (Chrisp, Drugs and Aging, 1991).

In summary, there is general agreement that patients at risk for clinical flare should be treated for flare prevention. Because of drug availability, most US studies have utilized non-steroidal anti-androgens (flutamide, bicalutamide, and nilutamide). Although these anti-androgens do have significant side effects (diarrhea, abdominal pain, and hepatic and

pulmonary toxicity), they are generally prescribed for only 2 to 3 weeks. Literature concerning the efficacy of various drugs used for flare prevention is controversial. No data exist which compare the efficacy and safety of GnRH antagonists with LHRH agonists with or without anti-androgens in patients at risk for the development of clinical flare.

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Appendix A – Clinical Trial **149-98-04 (Interim Analysis)** ("A Multi-center Study of Abarelix-Depot in Patients with Prostate Cancer in Whom GnRH Agonists are Contraindicated") Study initiation date: February 24, 1999. This study report is an interim analysis of data obtained through December 20, 1999, for patients first dosed on or before September 30, 1999.

A.1. Objective: The primary objective of this trial was the prevention of orchiectomy in patients with advanced prostate cancer symptoms during treatment with abarelix depot. Secondary objectives were to evaluate the safety of abarelix depot, its endocrinologic efficacy, and its effects on prostate specific antigen (PSA) kinetics.

A.2. Design and conduct summary: This was a multicenter, open-label study in which patients with advanced prostate cancer in whom GnRH agonists are contraindicated were to receive 7 doses of abarelix depot 100 mg by intramuscular injection on days 1, 15, 29, 57, 85, 113, and 141 for a treatment duration of 24 months. Eligible patients for study entry had 1 of the 4 following conditions secondary to prostate cancer: 1) bone pain from skeletal metastases 2) bilateral retroperitoneal adenopathy causing ureteral obstruction 3) impending neurological compromise and/or 4) the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction. Patients with known hormone-refractory prostate cancer or patients who had received prior hormonal therapy for metastatic prostate cancer or neoadjuvant hormonal therapy within 6 months before enrollment were excluded. Patients received their first dose of study drug on day 1 and then returned to the clinic for study assessments on days 2, 8, 15, 29, 57, 85, 113, 141, and 169. At the investigators' discretion, patients were permitted to continue to receive injections of study medication on day 169 and were to continue to report to the clinic every 28 days for dosing and assessments. The post-treatment period began 28 days after the last injection. Patients returned to the clinic for assessments 28 days after the last injection (end of treatment) and 4 to 5 weeks post-treatment (8 to 9 weeks after the last injection).

Reviewer's comment: GnRH agonists are not "contraindicated" in the 4 conditions listed above (bone pain from skeletal metastases, retroperitoneal adenopathy causing ureteral obstruction, impending neurological compromise, and the presence of an enlarged prostate gland or pelvic mass causing bladder outlet obstruction). Because of the testosterone "surge" seen with GnRH agonists, product labels state that patients with any of the 4 conditions listed should be "closely observed" during GnRH therapy.

Eighty-three patients were enrolled in the study. Fifty-seven had completed 85 days of treatment or had withdrawn from the study by December 20, 1999, and are included in this interim report. The treatment period consists of 100 mg abarelix-depot given on Days 1, 15, 29, 57, 85, 113, and 141. Patients could continue to receive abarelix-depot on Day 169 and every 28 days thereafter at the discretion of the investigator. Patients continuing on study on Day 169 were assessed for maintenance of castrate levels of testosterone. Patients who were castrate (testosterone levels <50 ng/dL) would continue to receive abarelix-depot at a dose of 100 mg IM on Day 169 and every 28 days thereafter. Patients not castrate on Day 169 (testosterone > 50 ng/dL) would be dosed with 100 mg on day

169, 2 weeks later on Day 183, and 2 weeks later on Day 197. Dosing would then be given on Day 225 and every 28 days thereafter.

At screening, symptomatic assessments were based on the patient's condition. Assessments for the specific problems occurring in each patient are listed below. Scans (ultrasound, CT, and bone) were repeated every 12 weeks.

- Bladder outlet obstruction:
  Urine flow, post-void residual, AUA symptom score, presence of catheter
- Cancer related bone pain
  VAS for pain and analgesic use, repeat bone scan every 12 weeks
- Cancer related pain
  VAS for pain and analgesic use
- Impending neurological compromise
  Detailed neurologic examination depending on the site of the lesion
- Bilateral or unilateral hydronephrosis
  Creatinine. Presence of stent. Renal ultrasound or CT scan every 12 weeks
- Azotemia
  Creatinine clearance, BUN as per scheduled chemistries

On Day 1 of treatment, patients had the following studies performed: hematology, chemistry, acid phosphatase, testosterone, LH, DHT, FSH, PSA, EQ-5D QOL questionnaire, SWOG 9039 questionnaire, and an endocrine questionnaire.

On Day 2, symptomatic assessment as applicable (see section under screening). Testosterone, DHT, LH, and FSH will be performed.

On Day 8, symptomatic assessment as applicable. Acid phosphatase, testosterone, DHT, LH, and FSH will be performed.

On Day 15, symptomatic assessment as applicable. Hematology, chemistry, acid phosphatase, testosterone, DHT, LH, FSH, PSA, EQ-5D, and SWOG 9039 will be performed.

On Days 29 and 57, symptomatic assessment as applicable. Hematology, chemistry, acid phosphatase, testosterone, DHT, LH, FSH, PSA, EQ-5D (day 57 only), SWOG 9039 (day 57 only) and endocrine questionnaire will be performed.

On Day 85, symptomatic assessment as applicable. All of the studies listed under days 29 and 57 will be repeated.

On Days 113 and 141, symptomatic assessment as applicable. Hematology, chemistry, acid phosphatase, testosterone, DHT, LH, FSH, PSA, and endocrine questionnaire will be performed.

On Day 169, symptomatic assessment as applicable. All of the studies listed under days 15 and 57 will be repeated.

For patients continuing treatment after 169 days, all day 169 evaluations will be performed every 28 days.

At follow-up (8 to 9 weeks after last injection), all studies listed under Days 15 and 57 will be repeated.

A.3. Study population: A total of 83 patients were enrolled in the study. Fifty-seven patients have completed 85 days of treatment and are included in the safety population at the time of this interim report. The remaining 26 patients will be included in the final study report submitted as part of the safety update. All 9 patients from a single study site in Mexico (site 499) were excluded from the intent-to-treat (ITT) population because of "regulatory noncompliance" at that site, resulting in a total of 48 ITT patients for this interim analysis.

A summary of baseline demographic data is presented in Table 1.

Table 1. Baseline demographic data

	Abarelix N = 48)
Race/ethnicity	N (%)
Caucasian	41 (85%)
African American	5 (10%)
Hispanic	2 (4%)
Age (yr)	
Median (range)	72 (40-94)

The symptomatic condition for study entry, Gleason grade, and baseline PSA are presented in Table 2.

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Table 2. Symptomatic condition for study entry, Gleason grade, and baseline PSA. (Patients may appear in more than one category.)

	Abarelix N = 48
Gleason grade	
2-4	4 (8%)
5-6	6 (13%)
7	9 (19%)
8-10	23 (48%)
unknown	6 (13%)
Baseline PSA (ng/mL)	
<20	9 (19%)
>20 and <100	16 (33%)
>100 and <1000	16 (33%)
>1000	7 (15%)
Symptomatic condition for study entry	
Bone pain from skeletal metastases	24 (50%)
Impending neurological compromise	4 (8%)
Ureteral obstruction	7 (15%)
Enlarged prostate or pelvic mass	13 (27%)

A.4. Inclusion and exclusion criteria: Inclusion criteria included:

1) male patient > 18 years of age
2) diagnosis of advanced, life-threatening, symptomatic prostate adenocarcinoma based on histological evidence or on clinical suspicion with an elevated PSA or acid phosphatase measurement. Advanced, life-threatening, symptomatic prostate cancer was defined as 1 or more of the following:
   - bone pain from prostate cancer skeletal metastases that was expected to be exacerbated by administration of an LHRH superagonist
   - impending neurological compromise from spinal, spinal cord, or epidural metastases that could have worsened or advanced to spinal cord compression upon administration of an LHRH superagonist; patients with spinal cord compression may have required not only immediate hormonal therapy, but also urgent radiation therapy, urgent decompressive laminectomy, or other neurological procedures
   - bilateral retroperitoneal adenopathy with ureteral obstruction (with or without azotemia) that could have progressed to hydronephrosis, azotemia, or worsening obstruction upon administration of a LHRH superagonist
   - presence of an enlarged prostate gland or pelvic mass caused by prostate cancer that had caused bladder outlet obstruction that could have worsened or resulted in urinary retention upon administration of an LHRH superagonist
3) symptomatic prostate cancer and LHRH superagonist therapy was otherwise contraindicated.
4) bilateral orchiectomy was the only treatment option and was unacceptable to the patient