4.2.3. ELISA for detection of IgG antibodies to abarelix

The sponsor used an ELISA similar to that used to detect IgE antibodies to detect IgG antibodies to abarelix. Patient samples were diluted 1:100 for this assay. The sponsor previously completed these assays and submitted results to the NDA in December, 2000. No abarelix-specific IgG antibodies were detected. These data were not resubmitted in this submission [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 157].

4.2.4. ELISA for detection of IgE antibodies to CMC

The sponsor used — filter paper disks to immobilize CMC. Patient samples were diluted 1:10 and incubated with the CMC-bound disks in a filter plate. After washing the disks, the amount of captured IgE was measured with an enzyme-linked anti-human IgE antibody. The positive control was serum from an individual sensitive to house dust mite allergen and dust mite allergen-coupled disks because no human antiserum containing IgE specific to CMC was available. The positive control yielded a signal — that of the negative control [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 157-158].

4.2.5. ELISA for detection of IgG antibodies to CMC

This assay was identical to that described above for the detection of IgE antibodies to CMC, except the amount of captured IgE was measured with an enzyme-linked anti-human IgG antibody. The positive control was serum from an individual sensitive to house dust mite allergen and dust mite allergen-coupled disks because no human antiserum containing IgE specific to CMC was available. The positive control yielded a signal — that of the negative control [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 158].

4.2.6. ELISA for detection of total IgE levels

Anti-human IgE was coated to the surface of a microtiter plate and exposed to patient samples. After washing, an alkaline phosphatase-conjugated secondary antibody specific to human IgE was added. PNPP was used as a color agent. Pooled normal human serum was used as assay controls, and total IgE content was determined by comparison of samples with a standard curve prepared by a serial dilution of IgE stock of known concentration. The standard curve covered the range of — mcg/mL. Patient samples were diluted 1:10. This assay was used to determine whether retained samples contain intact, assayable IgE and to detect those patients who had abnormally high levels [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 158].

4.2.7. ELISA for detection of total IgG levels

This assay was similar to that used to detect total IgE levels. Anti-human IgG was coated to the surface of a microtiter plate and exposed to patient sample. After washing, an alkaline phosphatase-conjugated secondary antibody specific to human IgG was added. PNPP was used as a color agent. Pooled normal human serum was used as assay controls, and total IgE content was determined by comparison of samples with a standard curve prepared by a serial dilution of IgG stock of known concentration. The standard curve covered the range of — mcg/mL. Patient samples were diluted 1:250,000. This assay was used to determine whether retained samples contain intact, assayable IgG [NDA 21-320, N000 AZ, 2/25/03, Volume 26, page 159].

4.3. Results of in vitro tests

Results of assays presented in this submission are reviewed below.

4.3.1. Abarelix IgE RIA

For the abarelix IgE RIA, none of the samples from abarelix-treated patients with allergic reactions fell outside of the upper 3 standard deviation limit. Changes in specific IgE levels between the pre-and post-treatment samples for abarelix-treated patients with allergic reactions were not different from patients who did not have allergic reactions. Changes in specific IgE levels between the pre-and post-treatment samples for abarelix-treated patients with allergic reactions were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 162-163].

4.3.2. Abarelix IgE ELISA

For the abarelix IgE ELISA, there was one post-event sample from an abarelix-treated patient who experienced redness of the hands on Day 57. He did not have an immediate onset reaction. His symptoms resolved and the patient remained on study drug. None of the other samples from abarelix-treated patients with allergic reactions fell outside of the upper 3 standard deviation limit. There was a baseline sample from an abarelix non-reactor and a baseline sample from a leuprolide-treated non-reactor who also had elevated levels of abarelix-specific IgE. Changes in specific IgE levels between the pre-and post-treatment samples for abarelix-treated patients with allergic reactions otherwise were not different from abarelix-treated patients who did not have allergic reactions. Changes in specific IgE levels between the pre-and post-treatment samples were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 164-165].

4.3.3. CMC IgE ELISA

For the CMC IgE ELISA, there was one pretreatment sample from a leuprolide-treated patient who did not have a reaction that fell outside of the upper 3 standard deviation limit. There was one post-treatment sample above the upper 3 standard deviation limit in one abarelix nonreactor. None of the samples from abarelix-treated patients with allergic reactions fell outside of the upper 3 standard deviation limits. Changes in specific IgE levels between the pre-and post-treatment samples for abarelix-treated patients with allergic reactions were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 166-167].

4.3.4. CMC IgG ELISA

For the CMC IgG ELISA, there were post-treatment samples from one leuprolide-treated patient who did not have a reaction and from two leuprolide-treated patients that had reactions that fell outside of the upper 3 standard deviation limit. There was one post-treatment sample above the upper 3 standard deviation limit in one abarelix nonreactor. None of the samples from abarelix-treated patients with allergic reactions fell outside of the upper 3 standard deviation limits. Changes in specific IgG levels between the pre- and post-treatment samples were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 168-169].

4.3.5. Total IgE ELISA

Two patients from the abarelix-treated group with allergic reactions had baseline and post-treatment IgE levels that were below the limit of quantitation for the assay. Levels below the limit of the assay were also noted in a post-treatment sample of one abarelix-treated patient who did not have an allergic reaction, in pretreatment and post-treatment samples of two leuprolide-treated patients who did not have allergic reactions. There was one leuprolide-treated patient who had an allergic reaction who had a total IgE that fell outside of the upper 3 standard deviation limit. Changes in total IgE levels between the pre-and post-treatment samples were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 170-171].

4.3.6. Total IgG ELISA

There were two samples, one pre-treatment and one post-treatment, in abarelix-treated patients who had allergic reactions that had total IgG levels that fell outside of the upper 3 standard deviation limit. There was one post-treatment sample in one abarelix-treated patient who did not have an allergic reaction at had total IgG levels that fell outside of the upper 3 standard deviation limit. Changes in total IgG levels between the pre-and post-treatment samples for abarelix-treated patients with allergic reactions were similar among treatment groups [NDA 21-320, N000 AZ, 2/25/03, Volume 26, pages 172-173].

5. UPDATED INTEGRATED SUMMARY OF SAFETY

A review of the sponsor's updated Integrated Summary of Safety follows.

5.1. Summary

The sponsor notes that approximately 1% of patients in both the pooled leuprolide and goserelin groups (3/484, 0.6%) and abarelix group (17/1397, 1.2%) were withdrawn from study drug due to allergic signs/symptoms or allergic reactions. The sponsor notes that the proportion of patients withdrawn due to an immediate onset systemic allergic event was 0% for active control and 0.43% for abarelix and that the proportion of injections associated with an immediate onset allergic systemic allergic event was 0% for active control and 0.038% for abarelix [ISS Update, 5/8/03, pages 196-198].

The sponsor's definition of allergic reactions includes both patients with immediate reactions and patients with delayed reactions and minimizes one of the critical differences between the patient groups—there were reactions with immediate onset in the abarelix group but there were no such reactions in the active control groups. The sponsor's analysis also excludes patients who had immediate onset of flushing, erythema, rash, urticaria, or pruritus without hypotension or syncope from the immediate onset allergic reaction group and also minimizes the difference between the treatment groups in the frequency of immediate onset reactions.

5.2. Exposure

Exposure to study treatment in Praecis-sponsored abarelix clinical trials is displayed in Table 3. There was a total of 1397 patients exposed to abarelix, 484 patients exposed to leuprolide, and 90 patients exposed to goserelin (Table 1) [ISS Update, 5/8/03, page 195].

This represents an additional 281 patients exposed to abarelix and 117 patients exposed to leuprolide since the review of the original NDA that are reported in this resubmission.

Table 3. Patients exposed, Praecis-sponsored abarelix clinical trials [ISS Update, 5/8/03, page 195]

Study	Leuprolide depot	Leuprolide depot plus bicalutamide	Goserelin plus bicalutamide	Abarelix
149-97-04	0	0	0	263
149-98-02	89	0	0	180
149-98-03	0	83	0	168
149-98-04	0	0	0	81
149-99-03	195	0	0	387
ABACAS1	0	0	90	87
149-01-03	27	0	0	55
149-01-05	0	0	0	176
Subtotal	311	83	90	1397
Total	484		90	1397

In addition, there were two investigator-sponsored studies of abarelix depot performed in patients with prostate cancer. There were 54 men exposed in these studies. Data for these investigator-sponsored clinical trials is not included in the analysis of the frequency of these events [ISS Update, 5/8/03, pages 191-194, 196]

5.3. Sponsor's estimates of frequency of allergic events

The sponsor assessed the frequency of allergic reactions in clinical studies they sponsored using the following definitions [ISS Update, 5/8/03, pages 190, 194-195]:

- Allergic reactions
  - Considered by the sponsor to include patients withdrawing from the study because of flushing, erythema, rash, urticaria, pruritus, hypotension, or syncope, regardless of time of onset of reaction
- Immediate onset allergic reactions
  - Considered by the sponsor to include patients who had rapid onset of flushing, erythema, rash, urticaria, pruritus with hypotension and syncope. This is a subset of the allergic reactions group.

Praecis reports that there were 20 patients who had allergic reactions in studies they sponsored. Of these 20 patients, 17 were treated with abarelix, two were treated with leuprolide, and one was treated with goserelin [ISS Update, 5/8/03, pages 198, 191-194].

There was one patient in one of the investigator-sponsored clinical trials of abarelix who had itching, flushing, and hives fifteen minutes after the fourth dose of abarelix. The event was treated with antihistamines and corticosteroids and resolved within one hour. There was also a patient who had swelling of the face and chin, and forearm eight hours after the first dose of abarelix. The patient was treated with an antihistamine [ISS Update, 5/8/03, page 190]. The sponsor did not include these patients in their analysis because they were not in a Praecis-sponsored study.

The sponsor notes that approximately 1% of patients in both the pooled leuprolide and goserelin groups (3/484, 0.6%) and abarelix group (17/1397, 1.2%) were withdrawn from study drug due to allergic signs/symptoms or allergic reactions, and that when duration of

exposure is considered, that the differences between the active control and abarelix groups are diminished.

The sponsor notes that the proportion of patients withdrawn due to an immediate onset systemic allergic event was 0% for active control and 0.43% for abarelix and that the proportion of injections associated with an immediate onset allergic systemic allergic event was 0% for active control and 0.038% for abarelix [ISS Update, 5/8/03, pages 196-198].

The sponsor estimates the proportion of patients withdrawn due to an allergic event per 100 patient-years of exposure was 0.62% for active control and 0.86% for abarelix. The sponsor notes that the incidence of allergic events in the active control and abarelix groups are similar when one limits allergic events to those that required medical intervention. They estimated the number of patients withdrawn due to an allergic event requiring concomitant medication for treatment to be 1.03 patients per 100 patient-years of exposure for active control and 0.98 patients per 100 patient-years for abarelix [ISS Update, 5/8/03, pages 196-198].

Reviewer comment:
There are two critical differences between the abarelix group and the control groups: (1) there were no reactions with immediate onset in the control groups but there were in the abarelix group, and (2) there were no immediate reactions associated with hypotension or syncope in the control groups but there were in the abarelix group. The sponsor's analysis minimizes these differences as described below.

The sponsor's definition of allergic reactions includes both patients with immediate reactions and patients with delayed reactions. It is likely that the mechanism of the immediate reactions and the delayed reactions is different. Importantly, the immediate allergic reactions are suggestive of an anaphylactic or anaphylactoid mechanism and have a potential for severe, life-threatening, or fatal outcomes. An analysis based on the sponsor's definition of allergic reactions minimizes one of the critical differences between the patient groups—there were reactions with immediate onset in the abarelix group but there were no such reactions in the active control groups.

The sponsor's analysis also excludes patients who had immediate onset of flushing, erythema, rash, urticaria, or pruritus without hypotension or syncope from the immediate onset allergic reaction group. Excluding this group is also inappropriate. These reactions are likely to be of the same mechanism, but of a lesser severity, as those associated with hypotension or syncope. Excluding this group also minimizes the difference between the treatment groups in the frequency of immediate onset reactions.

The sponsor's definition of an immediate onset systemic allergic event does not communicate that these events were associated with hypotension or syncope and obscures the other important difference between the abarelix and active control groups—there were immediate onset allergic events associated with hypotension or syncope in the abarelix group, but there were no such reactions in the active control groups.

This reviewer's analysis of the frequency of allergic events follows below.

6. REVIEWER'S ANALYSIS, FREQUENCY OF ALLERGIC EVENTS

6.1. Summary and conclusions

Immediate onset allergic reactions were noted in 1.1% of abarelix-treated patients, but there were none noted in patients treated with active control. The frequency of immediate onset allergic reactions with hypotension or syncope was 0.5%. There were no immediate onset allergic reactions with hypotension or syncope in patients treated with active control.

The per injection frequency of immediate onset allergic reactions associated with hypotension or syncope with abarelix of 0.04% is similar to penicillin and low osmolar radiocontrast media, but lower than that for hyperosmolar radiocontrast media. Penicillin and radiocontrast media are generally not used chronically and regularly, however. The most appropriate analysis for the frequency of allergic reactions for this drug is the life table analysis because of evidence that the frequency of reactions appears to increase over time and because the drug is to be used chronically and regularly. Updated estimates of the rates of immediate allergic reactions and immediate allergic reactions associated with hypotension or syncope after various periods of exposure may be found in the statistics review of this submission [NDA 21-320, N000 AZ, 2/25/03, Kate Meaker, M.S.].

6.2. Description of allergic reactions

An analysis of data for allergic events in the sponsor's clinical program was provided based on data included in the original NDA submission [Medical Officer consultation. Charles E. Lee, M.D., NDA 21-320, 4/20/01]. This analysis is updated below with data submitted with this submission. This analysis will address the frequency of the allergic reactions using the following definitions:

- Allergic reactions
  - Patients with flushing, erythema, rash, urticaria, pruritus, hypotension, or syncope, regardless of time of onset of reaction
- Delayed onset allergic reactions
  - Patients with flushing, erythema, rash, urticaria, pruritus, hypotension, or syncope with onset more than one hour after medication dosing
- Immediate onset allergic reactions
  - Patients with flushing, erythema, rash, urticaria, pruritus, hypotension, or syncope with onset less than one hour after medication dosing
- Immediate onset allergic reactions associated with hypotension or syncope
  - Patients with flushing, erythema, rash, urticaria, pruritus, that was associated with hypotension or syncope with onset less than one hour after medication dosing

A total of 21 patients had events that were suggestive of allergic reactions in Praecis-sponsored clinical studies. Of these 21 patients, 18 were treated with abarelix, 2 were treated with leuprolide, and 1 was treated with goserelin. The nature of the allergic reactions and relevant information for these 21 patients are summarized in Appendix 1. Patients who were excluded from the analysis because they had reactions that were not consistent with allergic reactions are summarized in Appendix 2.

As noted in the previous section, there was one patient in one of the investigator-sponsored clinical trials of abarelix who had itching, flushing, and hives fifteen minutes after the fourth dose of abarelix. The event was treated with antihistamines and corticosteroids and resolved within one hour. There was also a patient who had swelling of the face and chin, and forearm eight hours after the first dose of abarelix. This patient was treated with an antihistamine [ISS Update, 5/8/03, page 190]. The patients in the investigator sponsored studies are not included in the analysis below.

The allergic reactions seen in the abarelix-treated patients were consistent with the spectrum of symptoms and signs of systemic allergic reactions. Symptoms and signs in these patients included flushing, itching, urticaria, angioedema, hypotension, and syncope. One abarelix-treated patient developed "abnormal respirations" (not defined further) and was treated with bronchodilators, suggesting that bronchospasm may have been part of this patient's reaction. Immediate onset allergic reactions associated with syncope and/or hypotension were seen in 7 abarelix-treated patients. There was one abarelix patient that had a reaction associated with hypotension with the first dose. Seventeen of the 18 abarelix patients had reactions with the second or a later dose. Fourteen abarelix-treated patients developed reactions within five minutes of dosing. Fifteen abarelix-treated patients developed reactions within one hour of dosing. The timing of the reaction was not reported for one abarelix-treated patient. There were no leuprolide- or goserelin-treated patients with reactions associated with hypotension or syncope. There were no leuprolide- or goserelin-treated active control patients with reactions within the first hour of dosing. There were three active control patients that developed reactions several days after dosing. One leuprolide-treated patient reacted 4 days after the third dose and the other patient reacted 5 days after the first dose. The goserelin-treated patient developed a reaction 10 days after the second dose. No patient with a delayed onset allergic reaction had hypotension or syncope (Appendix 1).

The timing of the development of the allergic reactions in relation to the dosing of the drug is summarized in Table 4. As noted above, patients who had allergic reactions that occurred within one hour of dosing or were associated with hypotension or syncope were treated with abarelix. A rapid onset of reaction is typical of an IgE-mediated (Gell and Coombs type I) allergic reaction or an anaphylactoid reaction.

Table 4. Development of reactions in relation to dosing [Appendix 1]

Immediate onset allergic reactions (reactions occurring within an hour of dosing)					
Patient no.	**Study no.**	**Tab no.[1]**	**Treatment**	**Onset after dose**	**Syncope or hypotension**
11-2218	149-98-02	2	Abarelix depot	5 minutes	No
76-3224	149-98-03	3	Abarelix depot	Immediately	No
09-3246	149-98-03	4	Abarelix depot	Immediately	No
16-3028	149-98-03	6	Abarelix depot	5 minutes	No
357-2226	149-99-03	8	Abarelix depot	45 minutes	No
313-3087	149-99-03	9	Abarelix depot	5 minutes	Yes
333-3336	149-99-03	10	Abarelix depot	Immediately	Yes
401-4001	149-98-04	11	Abarelix depot	Within moments	Yes
409-4057	149-98-04	12	Abarelix depot	Immediately	No
416-4067	149-98-04	13	Abarelix depot	5 minutes	No
02-4635	149-97-04	14	Abarelix depot	2 minutes	No
29410085, DRO-JA	ABACAS1 extension	15	Abarelix depot	5 minutes	Yes
14070281, THY-JP	ABACAS1	16	Abarelix depot	One minute	Yes
01-2192	149-99-04	17	Abarelix depot	5 minutes	Yes
26860310	ABACAS1 Extension	23	Abarelix depot	2 minutes	Yes
Delayed onset allergic reactions (reactions occurring over an hour after dosing)					
Patient no.	**Study no.**	**Tab no.**	**Treatment**	**Onset after dose**	**Syncope or hypotension**
13-2144	149-98-02	1	Leuprolide depot	5 days	No
27-3200	149-98-03	5	Abarelix depot	NI[2]	No
301-1295	149-99-03	7	Leuprolide depot	Four days	No
7450299	ABACAS1	18	Goserelin plus bicalutamide	10 days	No
38-4700	149-97-04	19	Abarelix depot	3 days, 5 days	No
21540077	ABACAS1	20	Abarelix depot	The day after injection	No

[1] This reviewer's reference number
[2] NI = Not indicated

6.3. Frequency of allergic reactions

The frequency of systemic allergic reactions in the abarelix clinical program is displayed in Table 5. Eighteen cases of systemic allergic reactions were seen in 1397 abarelix-treated patients (one patient had 2 episodes on two different days of dosing), a frequency of 1.3%. There were 2 cases of systemic allergic reactions in 367 leuprolide-treated patients, a frequency of 0.4%, and there was 1 case of systemic allergic reaction in 90 goserelin-treated patients, a frequency of 1.1%. There were 15 cases of immediate systemic allergic reactions (developing within 1 hour of dosing) in the 1397 abarelix-treated patients, a frequency of 1.1%. In contrast, there were no immediate allergic reactions in the leuprolide- or goserelin-treated patients. There were 7 cases of immediate onset allergic reactions associated with hypotension or syncope in the abarelix-treated patients, a frequency of 0.5%. In contrast, there were no cases of such reactions in leuprolide- or goserelin-treated patients. Clearly, abarelix-treated patients developed immediate systemic allergic reactions at a greater frequency and severity than leuprolide- and goserelin-treated patients in these clinical studies.

Table 5. Frequency of allergic reactions, abarelix clinical studies [ISS Update, 5/8/03, pages 191-198].

Drug	N	Systemic allergic reactions		Delayed (>1hr) allergic reactions		Immediate (<1hr) allergic reactions		Immediate allergic reactions with hypotension or syncope	
		%	(n)	%	(n)	%	(n)	%	(n)
Abarelix	1397	1.3	(18)	0.2	(3)	1.1	(15)	0.5	(7)
Active control	574	0.5	(3)	0.5	(3)	0	(0)	0	(0)
Leuprolide	484	0.4	(2)	0.4	(2)	0	(0)	0	(0)
Goserelin	90	1.1	(1)	1.1	(1)	0	(0)	0	(0)

The sponsor makes a case for taking duration of exposure into account when calculating the frequency of these allergic events. The frequency of allergic reactions in abarelix clinical studies is displayed in Table 6. If one examines the frequency of allergic reactions per injection, the frequency of systemic allergic reactions is still greater for abarelix than for active control. More importantly, even if duration of exposure is factored into the calculation, cases of immediate allergic reactions or immediate allergic reactions with hypotension or syncope still only occurred in the abarelix-treated group.

Table 6. Frequency of allergic reactions, abarelix clinical studies [ISS Update, 5/8/03, pages 191-198; NDA 21-320, N000 BM, 5/16/03, Appendix 1, pages 1-2].

Drug	Injections	Systemic allergic reactions		Delayed (>1hr) allergic reactions		Immediate (<1hr) allergic reactions		Immediate allergic reactions with hypotension or syncope	
		%	(n)	%	(n)	%	(n)	%	(n)
Abarelix	15919	0.1	(18)	0.02	(3)	0.09	(15)	0.04	(7)
Active control	3789	0.08	(3)	0.08	(3)	0	(0)	0	(0)
Leuprolide	2833	0.07	(2)	0.07	(2)	0	(0)	0	(0)
Goserelin	956	0.1	(1)	0.1	(1)	0	(0)	0	(0)

Biometrics reviewer Kate Meaker previously performed a life table analysis of the incidence rates of allergic reactions based on data in the original NDA submission [NDA 21-320, Addendum to Statistical Review, dated 6/8/01, Kate Meaker, M.S.]. She found that the systemic allergic reaction event rates for abarelix-treated patients increased with drug exposure time. At one year the event rate was about 1.6% and at two years the event rate was about 4.1%. For patients with immediate allergic reactions associated with hypotension or syncope, the rate was 0.7% at one year and 1.1% approaching two years.

The most appropriate analysis for the frequency of allergic reactions for this drug is the life table analysis because of this evidence that the frequency of reactions appears to increase over time and because the drug is to be used chronically and regularly. Ms. Meaker is performing an updated life table analysis of the frequency of allergic reactions, based on the data in this submission. Updated estimates of the rates of immediate allergic reactions and immediate allergic reactions associated with hypotension or syncope after various periods of exposure may be found in her review of this submission.

6.4. Discussion

The sponsor argues that the frequency of allergic reactions is comparable to that seen with active control, based on calculations that take duration of exposure into account. As noted previously, this comparison is based on the rate of all allergic reactions, both

immediate and delayed. This comparison obscures the most important conclusion—that immediate onset allergic reactions, both with and without hypotension or syncope, occurred only in abarelix-treated patients and did not occur in patients treated with active control.

The sponsor also argues the frequency of allergic reactions associated with hypotension or syncope is comparable to other pharmaceuticals used in the management of prostate cancer by urologists and oncologists, such as paclitaxel, ACE inhibitors, protamine, radiocontrast media, sulfa antibiotics, penicillin, and cephalosporins. The sponsor concludes that urologists and oncologists are able to manage cases of immediate onset allergic reactions because they use these medications [Integrated Summary of Risk and Benefit, pages 100, 106].

The term anaphylaxis may be used to refer to immediate onset allergic reactions with multiple system involvement, such as urticaria, angioedema, hypotension, bronchospasm, shock, or circulatory collapse that are IgE-mediated. These reactions are immunologic in etiology and require prior sensitization, and would not cause a reaction upon first exposure. Anaphylactoid reactions refer to immediate onset allergic reactions with multiple system involvement, such as urticaria, angioedema, hypotension, bronchospasm, shock, or circulatory collapse that are not IgE-mediated and are not immunologic. Since sensitization is not required, anaphlyactoid reactions may occur with the first exposure to a drug.

The symptoms of anaphylactoid reactions and anaphylaxis are similar because the mediators of inflammation involved in both are the same. The onset is for both is commonly within one hour after administration of the drug and frequently may be within minutes of dosing. Treatment for both is the same, and includes epinephrine, H_1 and H_2 antihistamines, intravenous fluids, corticosteroids, and bronchodilators if the event is associated with bronchospasm.

The sponsor concludes that the reactions noted in the abarelix development program are anaphylactoid, or non-immune in character, based on skin testing and in vitro data. It should be noted that one patient had an immediate onset allergic reaction with the first exposure to abarelix, which suggests these reactions may be anaphylactoid in nature.

The sponsor's skin testing data indirectly supports the conclusion that the immediate onset reactions noted during the abarelix clinical development program were of an anaphylactoid or non-immune etiology. The in vitro tests suggest that the reactions noted in the clinical development program in abarelix-treated patients do not have an IgE or IgG-mediated etiology, and also provide indirect evidence that the reactions are anaphylactoid in nature. The sponsor has developed a skin testing protocol and in vitro tests of abarelix-specific IgE and IgG. If the product is approved, there may be some benefit in requesting the sponsor make a Phase 4 commitment to perform skin testing and in vitro testing of a defined number of patients who have such reactions to abarelix in the post-approval period, in order to further characterize the etiology of these reactions.

It is helpful to examine the frequency of anaphylaxis or anaphylactoid reactions for other drugs and biologics to provide a frame of reference for abarelix. Frequencies of anaphylaxis for penicillin and radiocontrast media are presented in Table 7. Penicillin is estimated to be responsible for 75% of anaphylactic deaths in the US. Frequencies of anaphylaxis range from 0.01% to 0.05% of all treatment courses for penicillin to 0.04% if all treatment courses of low osmolar radiocontrast media, to 0.22% of all treatment courses of hyperosmolar radiocontrast media [Lieberman, 1998; Adkinson, 1998; DrugDex®-Drug Evaluations, 2003]. The per injection frequency of anaphylaxis with abarelix of 0.04% was similar to penicillin and low osmolar radiocontrast media, but lower than that for hyperosmolar radiocontrast media. However, penicillin and radiocontrast media are generally not used chronically and regularly as abarelix is proposed for use. Because the drug is to be used chronically and regularly and because of the evidence that the frequency of reactions appears to increase over time, the life table analysis which expresses the frequency of reactions per patient at various points in time is the most appropriate analysis.

Table 7. Rates of anaphylaxis/anaphylactoid events for certain drugs [Lieberman, 1998; Adkinson, 1998; DrugDex®-Drug Evaluations, 2003]

Drug	Anaphylaxis/anaphlyactoid events, % of treatment courses		Fatal anaphylaxis, % of treatment courses
Penicillin	0.01 to 0.05	(anaphylaxis)	0.001-0.002
Low osmolar RCM	0.04	(anaphylactoid)	NA
Hyperosmolar RCM	0.22	(anaphlylactoid)	0.009

The sponsor argues that urologists and oncologists are able to manage cases of immediate onset allergic reactions because they use medications such as antibiotics or radiocontrast media. This is faulty reasoning. It is true that physicians administering parenteral antibiotics or radiocontrast media should be equipped and trained to treat immediate allergic reactions. However, the fact that these physicians administer these drugs does not prove that they are actually equipped or trained to treat such reactions.

7. RISK MANAGEMENT PLAN

The sponsor's risk management plan is reviewed below.

7.1. Summary and conclusions

The sponsor provided a risk management plan designed to insure that their product is used in a population where the benefit outweighs the risk. The risk management plan addresses labeling, patient and healthcare provider education, and includes a plan for evaluation of effectiveness. The sponsor's risk management plan appears to be acceptable from the clinical standpoint. The narrowed indication focuses on a population in which the risk of immediate allergic reactions is acceptable. The sponsor's plan to communicate appropriate risk and benefit information to healthcare providers and patients is comprehensive. The sponsor's plan to monitor the success of their risk management plan is appropriate. It is important that the details of components of this program communicate a fair balance of risk and benefit information. The content of proposed product labeling and sponsor communications to healthcare providers should emphasize the need for equipment and materials to treat allergic reactions and the need for the post-dose waiting period.

7.2. Contents of risk management plan

The Agency requested that the risk management plan achieve three objectives: (1) ensure that the product is used only in the indicated treatment population, (2) ensure that healthcare professionals are aware of the safety profile of the product, and (3) alert healthcare professionals to the potential for fluctuating testosterone levels and suggest periodic laboratory tests to monitor testosterone and PSA levels beyond six months of treatment to assess efficacy [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, page 32]. This risk management plan is being reviewed in depth by the Office of Drug Safety.

The sponsor's risk management plan consists of the following components:

1. Survey of current urologic practices regarding treatment of immediate onset systemic allergic reactions
2. Product labeling
3. Communications to healthcare professionals and patients
4. Evaluation of effectiveness of risk management plan
5. Distribution

Each of these components is reviewed briefly below. Specific comments on proposed product labeling are found in a following section of this document.

7.3. Survey of current urologic practices

The sponsor performed a survey of 33 urology practices to assess the current state of knowledge regarding treatment of immediate-onset allergic reactions [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, pages 34-35]. There were 11 physicians and 22 nurses or office managers interviewed. Of these 33 practices, 31 were office-based and two were hospital-based. Most practices had the equipment needed to treat immediate-onset allergic reactions. Antihistamines and intravenous fluids and apparatus were present in 85% of the practices surveyed; 79% of practices had epinephrine, antihistamines, intravenous fluids and apparatus, and epinephrine.

Practices were asked about a post-dose waiting period. Of these practices, 70% already administer treatments that require a post-dose waiting period. Nine of 11 physicians (81%) surveyed were willing to ask patients to remain in the office or healthcare facility for an observation period after treatment.

The sponsor concludes that the data suggest that the majority of practicing urologists are equipped to treat-immediate onset allergic reactions and that most patients would be compliant with an observation period following administration of a product that requires such an observation period. The sponsor also points out that they anticipate that their product will be administered most frequently in a hospital or an academic setting where equipment and materials necessary to treat allergic reactions would be readily available.

Reviewer comment:
It is encouraging that most of the practices surveyed had the equipment and medications necessary to treat allergic reactions and that most physicians were willing to ask patients to remain for a post-dose observation period. The content of proposed product labeling and sponsor communications to healthcare providers should emphasize the need for such equipment and materials and the need for the post-dose waiting period. Ideally, 100% of physicians administering this drug should have the equipment and materials necessary to treat allergic reactions.

7.4. Product labeling

In order to minimize risk and maximize benefit, the sponsor has included a boxed warning advising the provider of the risk for immediate-onset allergic reactions. The sponsor has also included a recommendation for an observation period after administration of the product in the label. Labeling advises the provider of the potential for the need to treat immediate-onset allergic reactions. The sponsor also will provide a patient package insert in Medication Guide format, written at the 8th grade reading level that emphasizes the importance of the observation period and identifies the symptoms of immediate-onset allergic reactions [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, pages 35-36].

Finally, the sponsor has narrowed the proposed indication to focus on a group of patients for whom the benefit of the drug is worth the risk of immediate allergic reactions. Previously, the proposed indication was [redacted] The drug is now proposed for use in patients with advanced symptomatic carcinoma of the prostate who have impending neurologic compromise from spinal, spinal cord, or epidural metastases, urinary tract obstruction from retroperitoneal adenopathy or from an enlarged prostate gland or pelvic mass, and/or bone pain from prostate cancer skeletal metastases requiring narcotic analgesia.

7.5. Communications to healthcare professionals and patients

The sponsor is proposing the following components of a program to communicate information to healthcare professionals and patient to ensure the product is used in a fashion to maximize benefit and minimize risk [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, pages 36-38]:

1. List of Frequently Asked Questions to be provided to patients
2. Open access website to provide information consistent with approved labeling for healthcare professionals and patients. There will be separate sections for professionals and patients.
3. A toll-free telephone number for healthcare professionals to provide guidance in the proper use of the product
4. A letter announcing the availability of the product with details on the appropriate patient population to receive the product. The letter is to be sent to a comprehensive list of potential prescribers.

5. Thirty educational programs within the first 12 months of market approval, each with a planned attendance of 10 healthcare professionals. These programs are to focus on the identification of the indicated treatment population and safeguards to prevent or treat potential serious adverse reactions.
6. Sales force outreach, including training of sales force emphasizing the importance of prescribing to the appropriate population and principal concepts of the risk management strategy. The sales force will focus on urologists and oncologists who see the highest number of patients in the indicated population. The sales force will instruct healthcare professionals to identify and properly treat those patients in the indicated population, to closely monitor patients for the occurrence of immediate allergic reactions to the product, and to administer effective treatment for a reaction, and to incorporate monitoring of testosterone and PSA levels. Instructions will reflect approved product labeling. Healthcare professionals will be encouraged to ensure that staff are appropriately trained and that equipment and materials are available for the treatment of immediate allergic reactions that may occur after administration of the product
7. Research articles regarding the safety profile of the product have been published and will continue to be published and disseminated to potential prescribers.
8. Advertising will be consistent with approved labeling and will present a fair balance of benefit and risk information
9. Product packaging will support labeling messages, and will include the package insert, a patient package insert, and the list of Frequently Asked Questions for patients.

Reviewer comment:
The sponsor's plan to communicate appropriate risk and benefit information to healthcare providers and patients is comprehensive. The proposed letter at launch, the proposed educational programs, and advertising must include a fair balance of risk and benefit information, however.

7.6. Evaluation of risk management plan

The sponsor will conduct knowledge, attitude, and practice surveys of a random sample of prescribing oncologists and urologists within 6 months of launch to determine the understanding and implementation of the risk management message. Data will be analyzed and shared with the Agency to determine whether further action is required [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, page 39].

The sponsor will collect, process, and evaluation all spontaneous adverse event reports received by their Pharmacovigiliance Department. A link to the FDA Form 3500 will be available on the Praecis website. A standard set of questions will be developed for use by the pharmacovigilance staff for handling allergic reaction reports [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, page 39].

Reviewer comment:
The sponsor's plan to monitor the success of their risk management plan is appropriate.

7.7. Distribution

The sponsor anticipates that distribution of their product will be to only those wholesalers and specialty pharmacies that service urologists, oncologists, and hospitals. The sponsor believes that formal limited or restricted distribution plan might limit access to the very patient population in which it is approved, as might happen with a patient who might present urgently to the Emergency Room with urgent symptoms [NDA 21-320, N000 AZ, 2/25/03, Risk Management Plan, pages 40-41].

Reviewer comment:
This reviewer concurs that a formal restricted distribution program would limit access for patients needing the product urgently.

The sponsor's skin testing data indirectly supports the conclusion that the immediate onset reactions noted during the abarelix clinical development program were of an anaphylactoid or non-immune etiology. The in vitro tests suggest that the reactions noted in the clinical development program in abarelix-treated patients do not have an IgE or IgG-mediated etiology, and also provide indirect evidence that the reactions are anaphylactoid in nature. The sponsor has developed a skin testing protocol and in vitro tests of abarelix-specific IgE and IgG. In order to further characterize the etiology of these reactions and as part of the risk management plan, consideration should be given to requesting the sponsor make a Phase 4 commitment to perform skin testing and in vitro testing of a defined number patients who have such reactions to abarelix in the post-approval period.

8. PROPOSED LABELING

Comments on specific points in the sponsor's proposed labeling follow below.

1. Black Box Warning

The text in the black box warning states the following:

[

]

Reviewer comments:
Although the sponsor's skin testing and in vitro data suggest an anaphlyactoid mechanism for the immediate allergic reactions, the data do not conclusively prove an anaphylactoid etiology.

. The words ' should be removed.

The reactions should be described as being characterized by flushing, itching, urticaria, hypotension, and/or syncope. The words — should be removed. Although the reactions noted in the development program were — most required treatment. Including the words — ' in the black box tends to minimize the message that reactions of this character may be life-threatening.

The incidence is described as 0.03% per injection. The incidence, if included in the black box warning, should be expressed from data from the life table analysis. The label should state the incidence per patient at 1 year of treatment and 2 years of treatment, similar to the manner that the risk for ischemic colitis is described in the Lotronex® label.

Trasylol® (aprotinin injection) may serve as a useful example for an acceptable boxed warning and WARNINGS section of the label. Trasylol® is a polypeptide proteinase inhibitor approved for use in cardiopulmonary bypass surgery. It, like abarelix, has been associated with immediate onset allergic reactions. The boxed warning recommends that the practitioner weigh the benefit of the drug with the risk of anaphylaxis before prescribing the drug. The WARNINGS section of the Trasylol® label addresses the incidence of immediate onset allergic reactions and notes the frequency at different degrees of exposure, and also notes the appropriate treatment for such reactions.

2. WARNINGS section of the label
The text in the black box warning is duplicated at the beginning of the WARNINGS section of the label.

Reviewer comment:
The bold type warning here should be the same as that described above in the black box warning.

The sponsor states that "transient, allergic skin reactions have been reported in 1% of patients treated with Plenaxis™. These have been characterized by 3 or more of the following signs/symptoms: generalized rash, urticaria, pruritus, tingling, and flushing. None were associated with systemic manifestation of allergy (e.g. bronchospasm, etc.). Reactions tended to occur rapidly (within minutes of injection). Skin reactions resolved spontaneously or with administration of oral steroids or antihistamines."

Reviewer comment:
The immediate skin reactions consisting of urticaria, pruritus, tingling, and flushing are systemic manifestations of allergy and represent reactions that are likely to be of the same etiology the ones that produced hypotension or syncope, but of a less severity. These immediate skin reactions should be described in the black box warning as noted above.

3. PRECAUTIONS General
The labeling states that patients treated with Plenaxis™ should be observed for symptoms of anaphylaxis for a brief interval immediately after drug administration. Labeling also states that if immediate onset hypersensitivity reactions occur (e.g. angioedema,

bronchoconstriction, hypotension, or syncope), appropriate medical treatment should be instituted and the drug discontinued.

Reviewer comment:
Labeling should state that patients should be observed for a defined period of time, such as 1 hour, after treatment. Itching, flushing, and urticaria should be included as additional immediate-onset hypersensitivity reactions.

4. ADVERSE REACTIONS section
This section also distinguishes between immediate onset allergic reactions with syncope and/or hypotension, as in the sponsor's proposed black box warning, WARNING, and PRECAUTIONS.

Reviewer comment:
The description of the character and frequency of immediate-onset hypersensitivity allergic reactions should include pruritus, flushing, and urticaria, as noted in reviewer comments above.

The sponsor's Table 3 summarizes the percentage of "allergic-type skin disorders" in their Phase 3 clinical trials, and includes the overall frequency of such reactions and frequencies of rash, pruritus, urticaria, dermatitis, and eczema.

Reviewer comment:
Patients who had immediate onset skin reactions should not be included in this table as they are likely to have a similar etiology as those who had hypotension and/or syncope. This table should be deleted.

9. REFERENCES

Adkinson NF. Drug allergy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St. Louis: Mosby; 1998. p. 1212-24.

DrugDex®-Drug Evaluations, http://csi.micromedex.com/, 2003.

Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St. Louis: Mosby; 1998. p. 1079-92.

10. APPENDICES

10.1. Appendix 1

Systemic allergic reactions, abarelix clinical studies [From sponsor's ISS and Correspondence, 4/6/01; ISS Update, 5/8/03]

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
13-2144	149-98-02	1	L	NI[4]	Pruritus, urticaria, maculopapular lesions	First, Day 1	5 days after dose	Benadryl	5 days	NI	Y	ISS
11-2218	149-98-02	2	A	71	Flushing, erythematous rash arms, chest, abdomen, back, pruritus	Second, Day 15	5 minutes after dose	Medrol	6-7 hours	Propine, Trusopt, Lansoprazole	Y	ISS
76-3224	149-98-03	3	A	NI	Tingling lower extremity, urticaria, pruritus of hands, palpitations	Third, Day 29	Immediately after dose	None	1 day	NI	Y	ISS
09-3246	149-98-03	4	A	81	Neck warm, itching left arm, urticaria trunk, neck and face, had RCM 2 hours prior to injection	Fifth, Day 85	Warm immediately, urticaria 15 minutes	None	Itching 30 min, urticaria 1 hour	Betopic RCM[5]	Y	ISS
27-3200	149-98-03	5	A	NI	Urticaria	Ninth, Day 197	NI	None	6 days	NI	Y	ISS
16-3028	149-98-03	6	A	NI	Generalized warmth, tingling, pruritus, erythema, [drug continued without recurrence]	NI Day 169	5 minutes	None	Same day	NI	N	ISS
301-1295	149-99-03	7	L	72	Numbness, swelling lip, red patches on palms 6 days after injection, 10 days after injection generalized urticaria, persistent rash	Third, Day 57	4 days	Epinephrine, Benadryl, famotidine, cetirizine, prednisone	12 days	Saw palmetto, MVI	Y	ISS
357-2226	149-99-03	8	A	NI	Generalized rash	NI Day 85	45 minutes	Benadryl	1 day	NI	Y	ISS
313-3087	149-99-03	9	A	74	Nausea, itching, syncope, incontinence, flushed, diaphoresis, thready pulse, hypotension,	Fourth, Day 57	5 minutes	Oxygen, iv fluids	40 minutes	Hyzaar, Cardura, Norvasc	Y	ISS
333-3336	149-99-03	10	A	72	Tingling fingertips, felt hot, labored breathing, syncope, incontinence, hypotension	Second, Day 15	Immediately	Iv fluids	3 hours	Oral RCM	Y	ISS

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
401-4001	149-98-04	11	A	85	Prickly all over, syncope, erythematous rash, hypotension, edema of wrists, ankles, periorbital, and around ears, abnormal respirations	Seventh, Day 141	Within moments	Oxygen, iv fluids, Epi, Benadryl, Solumedrol, albuterol,	4 hours	ASA, Proscar, atenolol, Vicodin, Vicoprofen	Y	ISS
409-4057	149-98-04	12	A	67	Warm neck, urticaria and pruritus of upper back, neck, chest	Third, Day 29	Immediately	None	Same day	Fentanyl, Percocet	Y	ISS
416-4067	149-98-04	13	A	64	Urticaria	Second, Day 15	5 minutes	Benadryl	Same day	NI	Y	ISS
02-4635	149-97-04	14	A	NI	Facial flushing	NI Day 676	2 minutes	None	30 minutes	NI	Y	ISS
DRO-JA 29410085	ABACAS1 extension	15	A	70	Felt warm, flushing face and chest, hypotension, generalized itching, hospitalized overnight	Fifteenth, Day 365	5 minutes	Intramuscular clemastine	1 hour	NI	Y	ISS, Response ISS update, page 193
THY-JP 14070281	ABACAS1	16	A	71	Face red and hot, changed vision, generalized rash, hypotension, elevated tryptase (20.2 mcg/l, 1.5 ULN)	First, Day 1	One minute	Iv clemastine	Same day	Perindopril, tolbutamide	Y	ISS, Response ISS update, page 192
01-2192	149-99-04	17	A	NI	Syncope, rapid respiration, flushing, generalized rash	NI Day 617	5 minutes	Oxygen, sq Benadryl	Same day	NI	Y	ISS
7450299	ABACAS1	18	G	70	Rash, pruritus on neck and ears	Second, Day 39	10 days	None	NI	Simvastatin Sotalol Chlorthalidone	Y	IR
38-4700	149-97-04	19	A	NI	Pruritus Rash Not reported as SAE	24th, Day 617 25th, Day 645	3 days[6] 5 days	Benadryl, topical HC	47 days 24 days	NI	Y	IR
21540077	ABACAS1	20	A	73	Cutaneous erythema, itching on extremities	Ninth, Day 229	The day after injection	NI	NI	Sotalol, Diltiazem, Haloperidol, pravastatin	Y	IR

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
26860310	ABACAS1 extension	23	A	NI	Hot flushes, dysaesthesia, hypotension (88/36), syncope, urinary incontinence, Discharged after 3 days	23[rd]	2 minutes	Iv fluids, iv hydrocortisone	3 days	NI	Y	Response ISS update, page 193

[1] This reviewer's reference number
[2] L = leuprolide depot, A = abarelix depot, G = goserelin plus bicalutamide
[3] ISS = sponsor's ISS, IR = Information request, Correspondence, Praecis, 4/6/01
[4] NI = Not indicated
[5] RCM = Radiocontrast media
[6] This patient had a reaction on two days, one on Day 617 and the second on Day 645

10.2. Appendix 2

Patients excluded from analysis because they were not likely to have had allergic reactions, Praecis-sponsored abarelix clinical studies [From sponsor's ISS and Correspondence, 4/6/01; ISS Update, 5/8/03]

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
377-3018	149-99-04	21	A	NI[4]	Syncope, "symptoms compatible with allergic reaction", CRF indicates only syncope [not suggestive of allergic reaction]	Tenth, Day 223	NI	Oxygen	NI	NI	Y, voluntary	Response ISS update, page 189; CRF
16-3029	149-99-03	22	L	NI	Syncope ("fainting"), no other symptoms noted, needed hospitalization, history of arrhythmia, stroke, diabetes mellitus [not suggestive of allergic reaction]	Tenth, NI	16 days	NI	NI	NI	Y	Response ISS update, page 189
038-4776	149-99-04	24	A	NI	Itching and rash under chin at site of prior folliculitis [not suggestive of allergic reaction]	21st, 22nd, 23rd, 24th	3-4 hours to 48 hours	Hydrocortisone cream	NI	NI	Y	Response ISS update, page 194; Study report 149-01-06, pages 31-32

[1] This reviewer's reference number
[2] L = leuprolide depot, A = abarelix depot, G = goserelin plus bicalutamide
[3] ISS = sponsor's ISS, IR = Information request, Correspondence, Praecis, 4/6/01
[4] NI = Not indicated

Reviewed by:

/S/

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

/S/

Lydia Gilbert-McClain, M.D.
Acting Medical Team Leader, Division of Pulmonary and Allergy Drug Products

/S/

Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Drug Products

cc: Division File, NDA 20-321
HFD-580/Monroe/Medical Team Leader
HFD-580/Hirsch/Medical Team Leader
HFD-715/Meaker/Statistics Reviewer
HFD-580/Shames/Division Director
HFD-580/Crisostomo/Project Manager
HFD-570/Lee/Medical Reviewer
HFD-570/Gilbert-McClain/Acting Medical Team Leader
HFD-570/Chowdhury/Division Director

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Lee
7/2/03 02:21:02 PM
MEDICAL OFFICER

Lydia McClain
7/2/03 02:45:36 PM
MEDICAL OFFICER

Badrul Chowdhury
7/2/03 03:20:21 PM
MEDICAL OFFICER

MEMORANDUM

Date: April 20, 2001

To: Mark Hirsch, M.D.
Medical Team Leader, Division of Reproductive and Urologic Drug Products

From: Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products

Badrul A. Chowdhury, M.D., Ph.D.
Medical Team Leader, Division of Pulmonary and Allergy Drug Products

Through: Robert J. Meyer, M.D.
Director, Division of Pulmonary and Allergy Drug Products

Subject: Consultation regarding allergic reactions noted in clinical trials conducted to gain marketing approval of abarelix (PLENAXIS

General Information

NDA#:	N21-320
Sponsor:	Praecis
Drug Product:	Abarelix for suspension
Request from:	Division of Reproductive and Urologic Drug Products (DRUDP)

Materials submitted: Sponsor's ISS; description of the allergic events seen in clinical trials; MedWatch reports of some of the cases; Consultative review of OPDRA on postmarketing reports of allergic reactions seen with currently marketed GnRH inhibitors; Correspondence from Praecis dated 4/6/01, submitted in response to IR from DRUDP.

1. INTRODUCTION

The Division of Reproductive and Urologic Drug Products (DRUDP) has consulted the Division of Pulmonary and Allergy Drug Products (DPADP) for evaluation and recommendations on the occurrence of allergic reactions seen in clinical trials with abarelix. DRUDP has specifically asked DPADP to assist with the following:

1. better understanding of the pathophysiology of the allergic reactions seen in the abarelix clinical program
2. overall impression on the clinical significance of these reactions, taking into account the symptom complex and incidence
3. opinion on a quantitative comparison to the currently marketed gonadotropin releasing hormone GnRH inhibitors, e.g., leuprolide

The sponsor contends that: (a) the incidence of allergic events seen in the clinical program was low; (b) the incidence of such events is comparable to that seen with leuprolide; and (c) the risk of allergic reaction can be managed with appropriate warnings in the label. We do not agree with the sponsor's view, based on our review of the submitted material. The allergic reactions are of concern, and should be given serious consideration.

2. ABARELIX

The abarelix drug substance is a synthetic decapeptide with a molecular weight of 1,416.06. The abarelix drug product is a suspension intended for intramuscular injection. It is initially manufactured as an abarelix-acetate water complex and converted to an abarelix-carboxymethylcellulose water complex during manufacture of the drug product. There may be small amounts of free carboxymethylcellulose (CMC) in addition to the abarelix-CMC in the product. The only other excipient in the drug product is 0.9% NaCl [Personal communication, Dr. De, Chemistry reviewer, 4/19/01].

The proposed indication

The product is to be administered as intramuscular injection on days 1, 15, and 29 of the first month of treatment, and every 28 days thereafter.

Abarelix suppresses gonadotropin secretion by directly and competitively blocking GnRH receptors at the pituitary gland. Unlike the currently marketed GnRH inhibitors, abarelix does not produce an initial surge of gonadotropins. The sponsor believes that abarelix has some advantage over the currently marketed GnRH inhibitors, because the initial gonadotropin surge may result in unwanted adverse effects in some patients, such as vertebral compression fracture due to deterioration of vertebral metastases, urinary obstruction due to enlargement of tumor size, among others. The sponsor believes that the product offers an alternative for patients who do would not tolerate this initial gonadotropin surge, and for patients for whom other modes of therapy are contraindicated.

3. SUMMARY REVIEW OF THE ALLERGIC REACTIONS SEEN IN THE ABARELIX CLINICAL PROGRAM

The abarelix clinical program was relatively small, with a total of 1,116 patients exposed to abarelix, 367 patients exposed to leuprolide, and 90 patients exposed to goserelin (Table 1). Even in this small database, a total of 20 patients were reported to have systemic allergic reactions. Of these 20 patients, 17 were treated with abarelix, 2 were treated with leuprolide, and 1 was treated with goserelin. The nature of the allergic reactions and relevant information for these 20 patients are summarized in Appendix 1.

Table 1. Patients exposed, abarelix clinical trials [Correspondence, Praecis, 4/6/01, page 3]

Study	Leuprolide depot	Leuprolide depot plus bicalutamide	Goserelin plus bicalutamide	Abarelix
149-97-04	0	0	0	263
149-98-02	89	0	0	180
149-98-03	0	83	0	168
149-98-04	0	0	0	81
149-99-03	195	0	0	387
ABACAS1	0	0	90	87
Subtotal	284	83	90	1166
Total	367		90	1166

The allergic reactions seen in the abarelix-treated patients were consistent with the spectrum of symptoms and signs of systemic allergic reactions, including anaphylaxis. Symptoms and signs in these patients included flushing, itching, urticaria, angioedema, hypotension, and syncope. One abarelix-treated patient developed "abnormal respirations" (not defined further) and was treated with bronchodilators, suggesting that bronchospasm may have been part of this patient's reaction. Anaphylaxis, with syncope and/or hypotension, was seen in 6 abarelix-treated patients. Sixteen of the 17 abarelix patients had reactions with the second or a later dose. Thirteen abarelix-treated patients developed reactions within five minutes of dosing. All but 3 of the 17 abarelix-treated patients developed reactions within one hour of dosing. One abarelix-treated patient reacted the day after dosing (not specified further), and another developed reactions three days after the 24^{th} dose and five days after the 25^{th} dose (Appendix 1). The timing of the reaction was not reported for one abarelix-treated patient.

In contrast, the 2 leuprolide-treated patients and the single goserelin-treated patient had reactions limited to the skin, and did not have evidence of circulatory or respiratory signs or symptoms suggestive of anaphylaxis. These 3 patients developed reactions several days after dosing. One leuprolide-treated patient reacted 4 days after the third dose and the other patient reacted 5 days after the first dose. The goserelin-treated patient developed a reaction 10 days after the second dose (Appendix 1).

The timing of the development of the allergic reactions in relation to the dosing of the drug is summarized in Table 2. All patients who had allergic reactions that occurred within one hour of dosing were treated with abarelix. A rapid onset of reaction is typical of a drug-induced type I allergic reaction or an anaphylactoid reaction (to be discussed later in this document).

Table 2. Development of reactions in relation to dosing

Reactions occurring within an hour of dosing					
Patient no.	**Study no.**	**Tab no.[1]**	**Treatment**	**Onset after dose**	**Syncope or hypotension**
11-2218	149-98-02	2	Abarelix depot	5 minutes	No
76-3224	149-98-03	3	Abarelix depot	Immediately	No
09-3246	149-98-03	4	Abarelix depot	Immediately	No
16-3028	149-98-03	6	Abarelix depot	5 minutes	No
357-2226	149-99-03	8	Abarelix depot	45 minutes	No
313-3087	149-99-03	9	Abarelix depot	5 minutes	Yes
333-3336	149-99-03	10	Abarelix depot	Immediately	Yes
401-4001	149-98-04	11	Abarelix depot	Within moments	Yes
409-4057	149-98-04	12	Abarelix depot	Immediately	No
416-4067	149-98-04	13	Abarelix depot	5 minutes	No
02-4635	149-97-04	14	Abarelix depot	2 minutes	No
DRO-JA	ABACAS1	15	Abarelix depot	5 minutes	Yes
THY-JP	ABACAS1	16	Abarelix depot	One minute	Yes
01-2192	149-99-04	17	Abarelix depot	5 minutes	Yes
Reactions occurring over an hour after dosing					
Patient no.	**Study no.**	**Tab no.**	**Treatment**	**Onset after dose**	**Syncope or hypotension**
13-2144	149-98-02	1	Leuprolide depot	5 days	No
27-3200	149-98-03	5	Abarelix depot	NI[2]	No
301-1295	149-99-03	7	Leuprolide depot	Four days	No
7450299	ABACAS1	18	Goserelin plus bicalutamide	10 days	No
38-4700	149-97-04	19	Abarelix depot	3 days, 5 days	No
21540077	ABACAS1	20	Abarelix depot	The day after injection	No

[1] This reviewer's reference number
[2] NI = Not indicated

The frequency of systemic allergic reactions in the abarelix clinical program is shown in Table 3. Eighteen cases of systemic allergic reactions were seen in 1,166 abarelix-treated patients (one patient had 2 episodes on two different days of dosing), a frequency of 1.5%. There were 2 cases of systemic allergic reactions in 367 leuprolide-treated patients, a frequency of 0.5%, and there was 1 case of systemic allergic reaction in 90 goserelin-treated patients, a frequency of 1.1%. There were 14 cases of immediate systemic allergic reactions (developing within 1 hour of dosing) in the 1,166 abarelix-treated patients, a frequency of 1.2%. In contrast, there were no immediate allergic reactions in the leuprolide- or goserelin-treated patients (Table 3). There were 6 cases of anaphylaxis with hypotension or syncope in the abarelix-treated patients, a frequency of 0.5%. In contrast, there were no cases of anaphylaxis in leuprolide- or goserelin-treated patients (Tables 2 and 3). Clearly, abarelix-treated patients developed immediate systemic allergic reactions at a greater frequency and severity than leuprolide- and goserelin-treated patients in these clinical studies. Frequency is by definition a rate, and is synonymous with occurrences per unit of time.

Table 3. Frequency of allergic reactions, abarelix clinical studies

Drug	**N**	**Systemic allergic reactions**		**Delayed (>1hr) allergic reactions**		**Immediate (<1hr) allergic reactions**		**Anaphylaxis**	
		%	**(n)**	**%**	**(n)**	**%**	**(n)**	**%**	**(n)**
Abarelix	1166	1.5	(18)	0.3	(3)	1.2	(14)	0.5	(6)
Leuprolide	367	0.5	(2)	0.5	(2)	0	(0)	0	(0)
Goserelin	90	1.1	(1)	1.1	(1)	0	(0)	0	(0)

The sponsor makes a case for taking duration of exposure into account when calculating the frequency of these allergic events. Such a method of calculation may be confounded. If susceptible patients withdraw from a study because of a reaction, the incidence for this

reaction per duration of exposure decreases as the study duration increases, due to attrition of the susceptible patients. Therefore, occurrences should be considered independent of duration of exposure in this circumstance. Frequency is already a rate and is synonymous with occurrences per unit of time.

The sponsor points out that the percent occurrence of systemic allergic reactions for abarelix was similar to that seen with leuprolide and goserelin. Although this is true for overall systemic allergic reactions, it is not true for immediate systemic allergic reactions (occurring within 1 hour of dosing), or for anaphylaxis (Table 3). Both immediate allergic reactions and anaphylaxis occurred at relatively high frequencies with abarelix in these clinical studies, and neither was observed with leuprolide or goserelin.

4. RESPONSE TO DRUDP QUESTIONS

Responses to three questions posed by DRUDP are in the following sections.

4.1. Please provide a better understanding of the pathophysiology of the allergic reaction seen in the abarelix clinical program

Of the various types of immunologically mediated drug reactions, two types are relevant to this consult. They are anaphylaxis and anaphylactoid reaction.

Anaphylaxis is a type I immediate hypersensitivity reaction induced by a drug substance, its metabolite, or another component of the drug product. As a result of this interaction, cells such as mast cells and basophils bearing high affinity IgE receptors are activated and release histamine and other mediators. These mediators are responsible for the clinical manifestations of this type of drug reaction. Cutaneous manifestations such as urticaria and angioedema (or both) are the most common manifestations of allergic drug reactions. Sometimes the allergic reaction affects multiple organ systems and manifests as anaphylaxis. Drug-induced anaphylaxis may be manifest as diffuse urticaria, angioedema, laryngeal edema, bronchospasm, and/or hypotension, and may be fatal. Type I immediate hypersensitivity drug reactions typically occur within one hour after administration of the drug in individuals sensitized from prior exposure. In individuals who have not been sensitized to a drug from a prior exposure, Type I immediate hypersensitivity drug reactions generally occur 7 to 10 days into treatment [Adkinson, 1998; Bernstein, 1999; Chowdhury, 1998; Chowdhury and Lieberman, 1999].

Most drugs have a molecular weight of less than 1,000 D and are not able to elicit an immune response by themselves. These small-molecule drugs or their metabolites must bind to tissue or plasma protein to produce a complete antigen. The process is called haptenation. Penicillin is the most widely studied model of haptenation [Adkinson, 1998; Chowdhury, 1998]. Abarelix has a molecular weight of 1,416.06 D, which is in the general size range for haptens. Abarelix also is highly protein bound. Over 96% of the drug is bound to plasma proteins. It is conceivable that abarelix or one of its metabolites is acting as a hapten. The chemical class of abarelix is also relevant. Unlike penicillins and other small-molecule drugs, abarelix is a decapeptide. The number of amino acids is the appropriate size for presentation for immune recognition on the MHC class II molecule.

In the abarelix database, all reactions except one occurred after second or later dose, and most of the reactions occurred within an hour of dosing. This is suggestive of IgE-mediated type I hypersensitivity. Most of the patients had involvement of multiple organ systems, which is typical of anaphylaxis. The proposed route and dosing schedule of abarelix is likely to be very sensitizing. Allergic drug reactions are known to increase in frequency with intermittent, repeated, and parenteral administration of a drug.

An anaphylactoid reaction is caused by the direct degranulation of mast cells and basophils without activation of the IgE-receptor pathway. The symptoms of anaphylactoid reactions and anaphylaxis are similar because the same mediators are involved in both. Like type I immediate hypersensitivity drug reactions, the onset is commonly within one hour after administration of the drug. One characteristic of anaphylactoid reactions that distinguishes them from anaphylaxis is the first-dose phenomenon. Anaphylactoid reactions commonly occur with the first exposure to a drug, as opposed to IgE-mediated reactions, which require a sensitizing dose. Drugs commonly associated with anaphylactoid reactions include radiocontrast media, opioids, iron-dextran, and vancomycin [Adkinson, 1998; Bernstein, 1999; Lieberman, 1999; Chowdhury and Lieberman, 1999].

It is unclear whether abarelix may also be causing anaphylactoid reactions. One patient had an allergic type reaction after the first dose, however that reaction developed 5 days after dosing. Five days may be a sufficient period of time to allow IgE production. An anaphylactoid reaction could represent a potential second mechanism of reaction for abarelix, in addition to IgE-mediated anaphylaxis. A dual mechanism has been reported with vancomycin.

As noted earlier in this review, the abarelix drug product contains CMC. The abarelix drug substance or CMC are possible causes of the allergic events in these studies. CMC in the abarelix drug product used in the clinical studies ranged from 21 to 24 mg per dose [Personal communication, Dr. De, Chemistry reviewer, 4/19/01]. CMC has been described as causing anaphylactic reactions in patients receiving parenteral injections of triamcinolone acetonide [Patterson, 1995; Montoro, 2000; Schuster, 2000] and oral barium sulfate suspension [Muroi, 1997]. These patients in these references were noted to have positive skin tests to CMC. Skin tests to CMC were negative in normal controls.

4.2. Overall impression on the clinical significance of these reactions, taking into account the symptom complex and incidence

The frequency and severity of allergic reactions reported in the abarelix database is quite impressive. The sponsor argues that the frequency of allergic reaction is comparable to that seen with leuprolide, based on calculations that take duration of exposure into account. As discussed earlier, such an analysis is confounded because the rate may decrease due to attrition of susceptible patients. Therefore, occurrences should be examined independent of duration of exposure. The frequency of allergic reactions in abarelix-treated patients (calculated without considering the duration of exposure) was 1.5%, as compared to 0.5% for leuprolide-treated patients, and 1.1% for goserelin-treated

patients (Table 3). When one takes into consideration the timing of the reaction relative to dosing in the abarelix-treated patients, there were 14 cases where reactions occurred one-hour of dosing (frequency of 1.2%), compared to none in other treatment groups. Reactions that occur within an hour of dosing are likely to be anaphylactic or anaphylactoid. Furthermore, there were 6 cases of anaphylaxis with hypotension or syncope in the abarelix-treated patients (frequency of 0.5%), compared to none in leuprolide- or goserelin-treated patients (Table 2 and Table 3). Abarelix-treated patients clearly developed immediate systemic allergic reactions at a greater incidence and severity than leuprolide- and goserelin-treated patients in these studies. These reactions could have been fatal if patients did not receive immediate medical attention.

It is helpful to examine the frequency of anaphylaxis or anaphylactoid reactions for other drugs and biologics to provide a frame of reference for abarelix. Frequencies of anaphylaxis for some drugs and biologics commonly recognized as a cause of anaphylaxis or anaphylactoid reactions are presented in Table 4. Penicillin is estimated to be responsible for 75% of anaphylactic deaths in the US. Frequencies of anaphylaxis range from 0.01% of all treatment courses for penicillin to 11% to 12% of all treatment courses with Crotalidae antivenom [Lieberman, 1998; Adkinson, 1998; Nelson, 1998; DrugDex®-Drug Evaluations, 2001]. The frequency of anaphylaxis with abarelix was higher than penicillin, radiocontrast media, and even higher than black widow spider antivenom. This is rather alarming considering the size of the limited clinical database for abarelix. Furthermore, many of the patients who will ultimately be treated with abarelix will have other medical diseases due to elder status, and will be taking concomitant medications, some of which may increase the risk of anaphylaxis. The chronic, monthly parenteral dosing of abarelix will also complicate this issue, as patients will be repeatedly exposed and could become sensitized over time.

Table 4. Rates of anaphylaxis/anaphylactoid events for certain drugs [Lieberman, 1998; Adkinson, 1998; Nelson, 1998; DrugDex®-Drug Evaluations, 2001]

Drug	Anaphylaxis/anaphlyactoid events, % of treatment courses		Fatal anaphylaxis, % of treatment courses
Penicillin	0.01 to 0.05	(anaphylaxis)	0.001-0.002
Low osmolar RCM	0.04	(anaphylactoid)	NA
Hyperosmolar RCM	0.22	(anaphlylactoid)	0.009
Black widow spider anitvenom	0.54	(anaphylaxis)	NA
Antithymocyte globulin	2	(anaphylaxis)	NA
Allergen immunotherapy	2	(anaphylaxis)	NA
Crotalidae antivenom	11 to 12	(anaphylaxis)	NA

The patients who developed allergic reactions in the clinical program were quite ill with advanced prostate cancer. None of the patients were less than 64 years of age and some were older than 80 years. No deaths were reported in the clinical trials. This is not assuring, because these patients were treated under a controlled clinical setting with close observation and rapid intervention of anaphylaxis. It may be unreasonable to expect similar favorable outcomes outside of a clinical trial setting.

Certain concomitant medications have been noted to increase the risk for development of anaphylaxis or the risk of a poor outcome from anaphylaxis [Lieberman, 1998; Adkinson, 1998]. Drugs with beta-blocking activity were concomitant medications in 4 abarelix-treated patients who developed systemic allergic reactions. Beta-blockers have been recognized to augment the severity of anaphylaxis and may interfere with the ability to treat anaphylaxis. Another abarelix-treated patient was also being treated with an ACE-inhibitor. ACE-inhibitors are known to increase the risk for the development of anaphylaxis and may make patients more refractory to treatment. Some of the patients in the clinical trials were also taking narcotic analgesics. Narcotics directly provoke mast cell histamine release (anaphylactoid reaction), and could theoretically augment the risk and severity of anaphylaxis from abarelix. Such concomitant medication use would be common in actual clinical use of the drug.

As noted earlier in this review, it is possible that CMC or the CMC-abarelix complex is responsible for these systemic allergic reactions, and not abarelix itself. Table 5 displays the CMC content of the abarelix drug product and approved GnRH inhibitors.

Table 5. Carboxymethylcelluose (CMC) content of GnRH inhibitors [Personal communication, Dr. De, 4/19/01; PDR® Electronic Library, 2001].

Drug product	Drug substance	Total CMC per dose*, mg	Route of delivery
Abarelix suspension (Plenaxis	Abarelix	21-24	Intramuscular injection
Lupron Depot suspension, 3.75 mg	Leuprolide	5	Intramuscular injection
Lupron Depot suspension, 7.5 mg	Leuprolide	5	Intramuscular injection
Lupron Depot–3 month 11.25 mg	Leuprolide	7.5	Intramuscular injection
Lupron Depot–3 month 22.5 mg	Leuprolide	7.5	Intramuscular injection
Lupron Depot–4 month 30 mg	Leuprolide	7.5	Intramuscular injection
Lupron Depot-PED–7.5 mg, 11.25 mg, and 15 mg	Leuprolide	5	Intramuscular injection
Lupron Injection	Leuprolide	0	Subcutaneous injection
Lupron Injection Pediatric	Leuprolide	0	Subcutaneous injection
Cetrotide for Injection	Cetrorelix	0	Subcutaneous injection
Zoladex	Goserelin	0	Subcutaneous injection
Zoladex 3-month	Goserelin	0	Subcutaneous injection
Synarel Nasal Solution for Endometriosis	Nafarelin	0	Intranasal spray
Synarel Nasal Solution for Central Precocious Puberty	Nafarelin	0	Intranasal spray

*Includes free CMC and drug-bound CMC

The abarelix drug product used in the clinical program contained 21 mg to 24 mg of CMC per dose. CMC is an excipient for the leuprolide depot products, and ranges from 5 mg to 7.5 mg per dose, depending on the product. The immediate release leuprolide products (Lupron Injection, Lupron Injection Pediatric), Cetrotide, Zoladex, and Synarel products do not contain CMC.

All cases of immediate allergic reactions and all cases of anaphylaxis in the clinical studies occurred in abarelix-treated patients. No cases of immediate allergic reactions or anaphylaxis occurred in leuprolide depot-treated patients. Both abarelix and leuprolide

depot contain CMC. Based on these data, it is not possible to rule out CMC as the cause of these allergic reactions.

4.3. Please provide a quantitative and qualitative comparison to currently marketed GnRH agonists

Dr. Toyer of DDRE II performed a post marketing safety review of anaphylaxis for the currently approved GnRH inhibitors. The AERS database revealed 31 cases of anaphylaxis. The numbers of these cases for each of the GnRH inhibitors are shown in Table 5. Unfortunately, one cannot determine the frequency of such events from spontaneous reporting data.

Table 5. Postmarketing cases of anaphylaxis, GnRH inhibitors [OPDRA Postmarketing Safety Review, D010038, Dr. Toyer, 3/10/01].

Drug	Number of cases
Cetrorelix	0
Goserelin	4
Leuprolide	23
Nafarelin	4

Although the product labeling of four marketed GnRH inhibitors mentions the possibility of allergic reactions, anaphylaxis does not occur commonly. The cetrorelix label refers to a single patient in a clinical study who developed a severe anaphylactic reaction with cough, rash, and hypotension. Labeling for goserelin states that hypersensitivity reactions have been reported rarely. The label states that allergic reactions occurred at a frequency of 1% or greater in goserelin-treated women from all clinical trials. No comment is made on the frequency of allergic reaction in males in goserelin clinical trials. In the leuprolide depot labels there is no mention of allergic reactions or anaphylaxis occurring in clinical trials. There is reference to one case of anaphylaxis reported in the medical literature, and the labels state that symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported for leuprolide (an incidence rate of about 0.002% is noted only in the label for leuprolide depot 7.5 mg). Perhaps the most useful information on the incidence of anaphylaxis comes from the nafarelin label. This label states that "in formal clinical trials of 1,509 healthy adult patients, symptoms suggestive of drug sensitivity, such as shortness of breath, chest pain, urticaria, rash and pruritus occurred in 3 patients (approximately 0.2%)."

The clinical trial data from the labels for the currently approved GnRH inhibitors suggest that the frequency of anaphylaxis for abarelix is higher than those of the currently approved GnRH inhibitors. Qualitatively, the reactions to abarelix were more severe and potentially life threatening as compared to the currently approved GnRH inhibitors.

5. SUMMARY AND RECOMMENDATIONS

Frequent, severe, and life-threatening anaphylactic reactions were noted with abarelix during clinical trials. The frequency and severity of such events appears to be greater than that noted with currently marketed GnRH products. These reactions should be considered before arriving at a regulatory decision on the approvability of abarelix. The sponsor proposes to use label warnings to address the risk of anaphylaxis. It may be very difficult, perhaps impractical, to label a drug that can cause life-threatening anaphylaxis, because

anaphylaxis is an unpredictable event. Label warnings will not provide any guidance to the prescriber other than stating the risk and asking that the physician be ready to treat anaphylaxis. Off-label use should also be taken into consideration. Other GnRH-inhibiting products are indicated for conditions other than prostate cancer, and abarelix may also be used in those situations. One could consider approving abarelix with restricted distribution and with strict warnings if the drug is deemed to be essential.

The allergic reactions in the patients could have been from the abarelix drug substance or CMC. Checking for IgE specific for abarelix and for CMC and skin testing may be helpful in evaluating the mechanism of this reaction and identifying the responsible antigen. Recommendations for testing for IgE and for skin testing are discussed later in this section of the review.

If the reaction from abarelix is purely and only anaphylactoid, pretreatment with corticosteroid, ephedrine, and H1 and H2 antihistamines might be considered. The reported incidence of anaphylactoid reactions in patients who have previously reacted to ionic high-osmolar radiocontrast media is 16 to 44% without pretreatment. With pretreatment, and with the use of non-ionic radiocontrast media, the risk of anaphylactoid reactions is reduced to approximately 1% [Bernstein, 1999, Chowdhury and Lieberman, 1999]. Pretreatment has been poorly studied in patients with IgE-mediated disease, however, and this procedure may make an IgE-mediated event more difficult to treat because of masking symptoms and signs and thereby delaying treatment [Lieberman, 1998]. This procedure is also not practical for a drug administered on a monthly basis. For these reasons, pretreatment is not suitable for abarelix.

The sponsor should be advised to characterize the nature of the allergic reaction. The clinical presentations of these reactions are typical of IgE-mediated Type I hypersensitivity. The antigen may be abarelix, its metabolite, or even CMC. Establishing the mechanism of these allergic reactions can help to make a decision on the approvability of the drug more scientific and rational. The sponsor should be asked to check for IgE antibody in the serum to abarelix and CMC. The sponsor has not detected IgG antibody to abarelix in patient serum using an ELISA. The ELISA can be modified for detecting IgE antibody to abarelix. The sponsor should also develop an ELISA to detect IgE antibody to CMC.

In addition, the sponsor should skin test the patients who have been exposed to abarelix. Skin testing should be performed to abarelix drug substance alone, CMC alone, and the abarelix drug product. A dose titration skin test, similar to that in the product label for Hymenoptera venom [Venomil™ Package Insert, 1999] can be used to develop a skin test for abarelix. One should be aware that a negative skin test or ELISA might not be predictive for absence of an allergic reaction with subsequent exposure to the drug. It may be impossible to identify all possible haptenic forms that may form in vivo from abarelix.

A way forward for the sponsor may be possible if they can develop a sensitive and specific test (ELISA-based, or skin test) for IgE antibody to abarelix and to CMC. If

patients are found to be sensitive to the CMC component, and not to abarelix, then a path forward may be reformulation of the drug product to exclude CMC.

Another path forward may be possible if the patients are found to be sensitive to abarelix, but not to CMC. If patients who have developed an allergic reaction to abarelix were to test positive, and patients (and normal volunteers) who have never been treated with abarelix were to test negative, then patients who have been treated with abarelix and have not manifested any allergic reaction could be tested to establish the positive and negative predictive values of the test. If the predictive values of the test are high, then one could perform the test before every dosing with abarelix. A positive test would preclude further treatment. Currently, such skin testing is used in patients with suspected penicillin allergy, and before using horse-derived antisera such as anti-thymocyte globulin in patients with suspected allergy.

6. REFERENCES

American Academy of Allergy, Asthma, and Immunology. Practice parameters for the diagnosis and management of anaphylaxis. J Allergy Clin Immunol 1998; 101(Part 2): S465-S528.

Adkinson NF. Drug allergy. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St. Louis: Mosby; 1998. p. 1212-24.

Beaudouin E, et al. [Anaphylaxis caused by carboxymethylcellulose: report of 2 cases of shock from injectable corticoids]. Allerg Immunol (Paris) 1992; 24:333-5.

Bernstein IL, Gruchalla RS, Lee RE, et al.: Disease management of drug hypersensitivity: A Practice Parameter. Ann Allergy Asthma Immunol 1999; 83:665-700.

Chowdhury BA, Drug Reactions. In: Fitzgerald FF, ed. Current Practice of Medicine. Vol. 1, pp. 167-174, Current Medicine, Inc., Philadelphia, USA, 1998.

Chowdhury BA, Lieberman PL. Drug Allergens, Haptens and Anaphylatoxins. In: Lockey RF, Bukantz SC, Fernandez-Caldas E, ed. Allergens and Allergen Immunotherapy. 2nd edition. p. 273-296, WB Saunders, Philadelphia, USA, 1999.

DrugDex®-Drug Evaluations, http://tomescps.com/, 2001.

Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St. Louis: Mosby; 1998. p. 1079-92.

Montoro J, et al. Anaphylactic shock after intra-articular injection of carboxymethlycellulose. Allergol Immunolpathol (Madr) 2000; 28:332-3.

Muroi N, et al. Anaphylaxis from the carboxymethylcellulose component of barium sulfate suspension. N Engl J Med 1997; 337:1275-7.

Nelson H. Immunotherapy for inhalant allergens. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. Allergy: principles and practice. 5th ed. St. Louis: Mosby; 1998. p. 1050-62.

PDR Electronic Library, http://pdrel.com/, 2001.

Patterson DL, et al. Anaphylaxis induced by the caboxymethylcellulose component of injectable triamcinolone acetonide suspension (Kenalog). Ann Allergy Asthma Immunol 1995; 74:163-6.

Schuster C, et al. Anaphylaxis to E466. Allergy 2000; 55:303-4.

Venomil™ Package Insert, Hollister Stier Laboratories, LLC, http://www.hollister-stier.com/downloadable_literature.asp, 1999.

cc: Original NDA
HFD-580/Monroe/Medical Reviewer
HFD-580/Hirsch/Team Leader
HFD-580/Allen/Division Director
HFD-580/Best/Project Manager
HFD-570/Lee/Medical Reviewer
HFD-570/Chowdhury/Team Leader
HFD-570/Meyer/Division Director

Appendix 1. Systemic allergic reactions, abarelix clinical studies [From sponsor's ISS and Correspondence, Praecis, 4/6/01]

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
13-2144	149-98-02	1	L	NI[4]	Pruritus, urticaria, maculopapular lesions	First, Day 1	5 days after dose	Benadryl	5 days	NI	Y	ISS
11-2218	149-98-02	2	A	71	Flushing, erythematous rash arms, chest, abdomen, back, pruritus	Second, Day 15	5 minutes after dose	Medrol	6-7 hours	Propine, Trusopt, Lansoprazole	Y	ISS
76-3224	149-98-03	3	A	NI	Tingling lower extremity, urticaria, pruritus of hands, palpitations	Third, Day 29	Immediately after dose	None	1 day	NI	Y	ISS
09-3246	149-98-03	4	A	81	Neck warm, itching left arm, urticaria trunk, neck and face, had RCM 2 hours prior to injection	Fifth, Day 85	Warm immediately, urticaria 15 minutes	None	Itching 30 min, urticaria 1 hour	Betopic RCM[5]	Y	ISS
27-3200	149-98-03	5	A	NI	Urticaria	Ninth, Day 197	NI	None	6 days	NI	Y	ISS
16-3028	149-98-03	6	A	NI	Generalized warmth, tingling, pruritus, erythema, [drug continued without recurrence]	NI Day 169	5 minutes	None	Same day	NI	N	ISS
301-1295	149-99-03	7	L	72	Numbness, swelling lip, red patches on palms 6 days after injection, 10 days after injection generalized urticaria, persistent rash	Third, Day 57	4 days	Epi, Benadryl, famotidine, cetirizine, prednisone	12 days	Saw palmetto, MVI	Y	ISS
357-2226	149-99-03	8	A	NI	Generalized rash	NI Day 85	45 minutes	Benadryl	1 day	NI	Y	ISS
313-3087	149-99-03	9	A	74	Nausea, itching, syncope, incontinence, flushed, diaphoresis, thready pulse, hypotension,	Fourth, Day 57	5 minutes	Oxygen, iv fluids	40 minutes	Hyzaar, Cardura, Norvasc	Y	ISS
333-3336	149-99-03	10	A	72	Tingling fingertips, felt hot, labored breathing, syncope, incontinence, hypotension	Second, Day 15	Immediately	Iv fluids	3 hours	Oral RCM	Y	ISS
401-4001	149-98-04	11	A	85	Prickly all over, syncope, erythematous rash, hypotension, edema of wrists, ankles, periorbital, and around ears, abnormal respirations	Seventh, Day 141	Within moments	Oxygen, iv fluids, Epi, Benadryl, Solumedrol, albuterol,	4 hours	ASA, Proscar, atenolol, Vicodin, Vicoprofen	Y	ISS
409-4057	149-98-04	12	A	67	Warm neck, urticaria and pruritus of upper back, neck, chest	Third, Day 29	Immediately	None	Same day	Fentanyl, percocet	Y	ISS

Patient No.	Study No.	Tab No.[1]	Rx[2]	Age	AE	Dose	Onset	Rx of AE	Resolution	Concomitant medications	Withdrawn, Yes/No	Source of report[3]
416-4067	149-98-04	13	A	64	Urticaria	Second, Day 15	5 minutes	Benadryl	Same day	NI	Y	ISS
02-4635	149-97-04	14	A	NI	Facial flushing	NI Day 676	2 minutes	None	30 minutes	NI	Y	ISS
DRO-JA	ABACAS1	15	A	70	Felt warm, flushing face and chest, hypotension, generalized itching, hospitalized overnight	Fifteenth, Day 365	5 minutes	Im clemastine	1 hour	NI	Y	ISS
THY-JP	ABACAS1	16	A	71	Face red and hot, changed vision, generalized rash, hypotension, elevated tryptase (20.2 mcg/l, 1.5 ULN)	First, Day 1	One minute	Iv clemastine	Same day	Perindopril, tolbutamide	Y	ISS
01-2192	149-99-04	17	A	NI	Syncope, rapid respiration, flushing, generalized rash	NI Day 617	5 minutes	Oxygen, sq Benadryl	Same day	NI	Y	ISS
7450299	ABACAS1	18	G	70	Rash, pruritus on neck and ears	Second, Day 39	10 days	None	NI	Simvastatin Sotalol Chlorthalidone	Y	IR
38-4700	149-97-04	19	A	NI	Pruritus Rash Not reported as SAE	24th, Day 617 25th, Day 645	3 days[6] 5 days	Benadryl, topical HC	47 days 24 days	NI	Y	IR
21540077	ABACAS1	20	A	73	Cutaneous erythema, itching on extremities	Ninth, Day 229	The day after injection	NI	NI	Sotalol, Diltiazem, Haloperidol, pravastatin	Y	IR

[1] This reviewer's reference number
[2] L = leuprolide depot, A = abarelix depot, G = goserelin plus bicalutamide
[3] ISS = sponsor's ISS, IR = Information request, Correspondence, Praecis, 4/6/01
[4] NI = Not indicated
[5] RCM = Radiocontrast media
[6] This patient had a reaction on two days, one on Day 617 and the second on Day 645

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Lee
4/23/01 01:04:38 PM
MEDICAL OFFICER

Badrul Chowdhury
4/23/01 02:37:07 PM
MEDICAL OFFICER

Robert Meyer
4/23/01 02:52:49 PM
MEDICAL OFFICER

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

The Safety Update Review is included in the Integrated Review of Safety (see Medical Officer Review of Original NDA, pgs., 49-92).