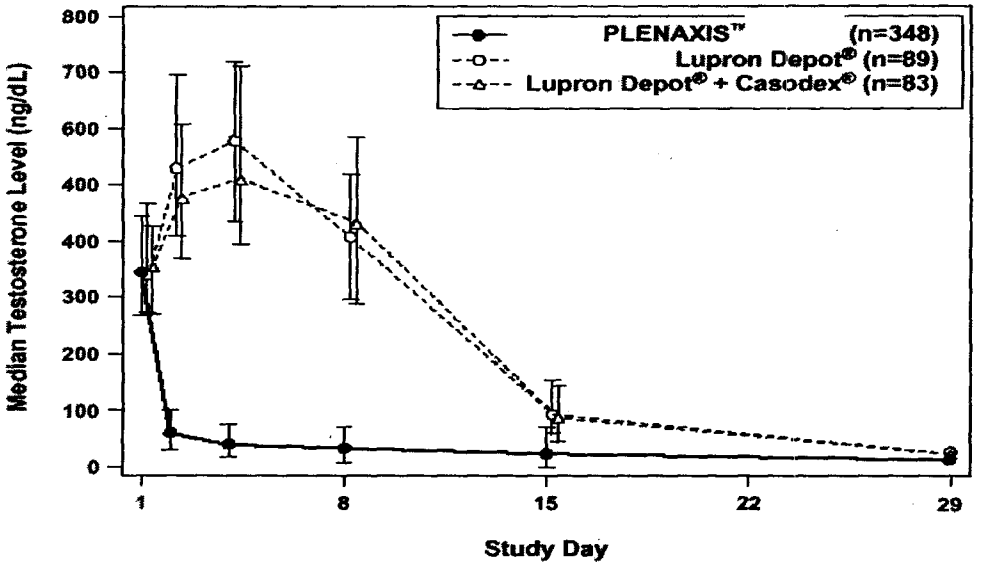
**Table 8. Median Serum Testosterone Levels**

| | Study 149-98-02 | | | | Study 149-98-03 | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron N = 89 | | Abarelix N = 180 | | Lupron + Casodex N = 83 | | Abarelix N = 168 | |
| Study Day | n | Median[1] (ng/dL) | N | Median (ng/dL) | N | Median (ng/dL) | n | Median (ng/dL) |
| Baseline | 89 | 338 | 180 | 350 | 83 | 353 | 167 | 340 |
| Day 2 | 87 | 529 | 178 | 59 | 81 | 480 | 166 | 58 |
| Day 4 | 84 | 578 | 173 | 37 | 79 | 512 | 160 | 40 |
| Day 8 | 82 | 406 | 175 | 29 | 79 | 435 | 164 | 35 |
| Day 15 | 88 | 94 | 179 | 20 | 81 | 90 | 168 | 23 |
| Day 29 | 88 | 15 | 179 | 11 | 81 | 16 | 168 | 10 |
| Day 57 | 85 | 10 | 174 | 12 | 80 | 10 | 167 | 9 |
| Day 85 | 86 | 9 | 176 | 15 | 80 | 10 | 164 | 14 |
| Day 113 | 84 | 8 | 173 | 11 | 76 | 8 | 161 | 9 |
| Day 141 | 83 | 8 | 169 | 13 | 70 | 11 | 157 | 11 |
| Day 169 | 81 | 9 | 166 | 15 | 69 | 10 | 155 | 11 |

Intent-to-treat population
[1] The lower limit of detection of the assay was 8 ng/dL; values below the detection limit are reported as 8 ng/dL.
Source: Derived from Table 12.5.7 in the 149-98-02 and 149-98-03 clinical study reports.

**Figure 3. Serum Testosterone Concentrations During the First 4 Weeks of Treatment with Abarelix, Lupron, or Lupron Plus Casodex**




**Bars represent the interquartile range.**

Source: Proposed label for Plenaxis (Vol 1.1, December 2000 submission).

### 8.4.2.1 Avoidance of Testosterone Surge

In Study 149-98-02, 82% of the patients in the Lupron group and none (0%) of the patients in the abarelix group experienced a testosterone surge ($p < 0.001$) (Table 9). Similarly, in Study 149-98-03, 86% of the patients in the Lupron plus Casodex group and none (0%) of the patients in the abarelix group experienced a testosterone surge ($p < 0.001$). Thus, across the 2 studies, all of the abarelix patients avoided a testosterone surge, while only 18% and 14% of the patients in the active control groups avoided a surge.

**Medical Officer's Comment**

- **Results from both of the pivotal efficacy studies support the Sponsor's claim that patients treated with abarelix did not experience the testosterone surge that occurs in a high percentage of patients at the onset of treatment with a superactive GnRH agonist.**

**Table 9. Percentage of Patients Who Experienced a Testosterone Surge**

| Study Endpoint | Treatment Group: Lupron N | Lupron n (%) | Lupron plus Casodex N | Lupron plus Casodex n (%) | Abarelix Depot N | Abarelix Depot n (%) | P-value[1] |
|---|---|---|---|---|---|---|---|
| 149-98-02 | | | | | | | |
| Experienced Surge[2] | 89 | 73 (82) | — | — | 180 | 0 | < 0.001 |
| Avoided Surge[2] | 89 | 16 (18) | — | — | 180 | 180 (100) | |
| 149-98-03 | | | | | | | |
| Experienced Surge[2] | — | — | 83 | 71 (86) | 168 | 0 | < 0.001 |
| Avoided Surge[2] | — | — | 83 | 12 (14) | 168 | 168 (100) | |

Intent-to-treat population
[1] Fisher's exact test
[2] Testosterone surge is defined as testosterone value that exceeded baseline by ≥ 10% on any 2 of days 2, 4, or 8. Avoidance of surge was defined as the absence of testosterone surge.
Source: Derived from Table 12.4.2.1 in the 149-98-02 and 149-98-03 clinical study reports.

### 8.4.2.2 Rapidity of Medical Castration

The endpoint for rapidity of medical castration was defined as a serum testosterone value ≤ 50 ng/dL on Study Day 8. No patients in the active control groups were medically castrate on Day 8 compared with 72% and 68% of the patients in the abarelix group in Studies 149-98-02 and 149-98-03, respectively ($p < 0.001$; Table 10). Twenty-four percent (24%) of the patients in each of the abarelix groups were medically castrate by Study Day 2. No patients in the active control groups in either study were medically castrate on Study Day 2.

**Medical Officer's Comment**

- **Results from both of the pivotal efficacy studies support the Sponsor's claim that serum testosterone levels are suppressed to ≤ 50 ng/dL within 8 days of the onset of treatment in a statistically significant greater proportion of patients treated with abarelix compared to patients treated with Lupron or Lupron plus Casodex.**

**Table 10. Percentage of Patients with Testosterone ≤ 50 ng/dL (Medically Castrate) on Study Days 2, 8, 15, and 29**

| | Treatment Group | | | | | | |
|---|---|---|---|---|---|---|---|
| | Lupron | | Lupron plus Casodex) | | Abarelix | | |
| | N | Castrate n (%) | N | Castrate n (%) | N | Castrate n (%) | P-value[1] |
| | Study 149-98-02 | | | | | | |
| Day 2 | 87 | 0 | — | — | 176 | 43 (24) | < 0.001 |
| Day 8 | 89 | 0 | — | — | 180 | 129 (72) | < 0.001 |
| Day 15 | 88 | 9 (10) | — | — | 179 | 134 (75) | < 0.001 |
| Day 29 | 88 | 86 (98) | — | — | 179 | 167 (93) | ND |
| | Study 149-98-03 | | | | | | |
| Day 2 | — | — | 80 | 0 | 163 | 39 (24) | < 0.001 |
| Day 8 | — | — | 83 | 0 | 168 | 114 (68) | < 0.001 |
| Day 15 | — | — | 81 | 17 (21) | 168 | 119 (71) | < 0.001 |
| Day 29 | — | — | 81 | 79 (98) | 168 | 160 (95) | ND |

Intent-to-treat population
[1] Fisher's exact test
Source: Table 12.4.3.1 (days 2-8) and Table 12.4.4 (days 15 and 29) in the 149-98-02 and 149-98-03 clinical study reports.

### 8.4.2.3 Achievement and Maintenance of Medical Castration From Day 29 Through Day 85

The primary efficacy endpoint for the achievement and maintenance of medical castration in the pivotal studies required a serum testosterone concentration of ≤ 50 ng/dL on Day 29 with no two (2) consecutive testosterone measurements > 50 ng/dL 2 weeks apart between Days 29 and 85, inclusive (Protocol Definition No. 2). The analysis for this endpoint was based on the ITT population using straightforward proportions with the LOCF. In Study 149-98-02, medical castration was achieved and maintained by 95.5% of the active control group and 91.7% of the abarelix group. In Study 149-98-03, medical castration was achieved and maintained by 95.2% of the patients in the Lupron plus Casodex group and 92.9% of those in the abarelix group (Table 11). The point differences between successful achievement of the primary efficacy endpoint in each of Studies 149-98-02 and 149-98-03 were –3.8% and –2.3 %, respectively, both in favor of the active control treatment. The lower bounds of the two-sided 95% confidence intervals for the differences in achievement and maintenance of medical castration were -9.7% in Study 149-98-02 and -8.4% in Study 149-98-03. The upper bounds of the confidence intervals for both differences crossed 0. Thus, treatment with abarelix met the agreed upon criteria for noninferiority compared to treatment with Lupron or Lupron plus Casodex in the pivotal efficacy studies.

In Study 149-99-03 (a supportive but not a pivotal efficacy trial), medical castration was achieved and maintained by 97.4% of the patients in the Lupron group and 89.7% of the patients in the abarelix group, a difference of –7.7%. The lower bound of the two-sided 95% confidence interval for this difference was -11.5%, slightly outside of the predefined lower bound of -10.0% required for noninferiority.

**Table 11. Percentage of Patients Who Achieved and Maintained Medical Castration From Day 29 Through Day 85 (No Two Consecutive Testosterone Values > 50 ng/dL)**

| | Treatment Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron | | Lupron plus Casodex | | Abarelix | | Percent Difference | |
| | N | Percent | N | Percent | N | Percent | Value | 95% CI[1] |
| 149-98-02 | 89 | 95.5 | — | — | 180 | 91.7 | -3.8 | (-9.7, 2.1) |
| 149-98-03 | — | — | 83 | 95.2 | 168 | 92.9 | -2.3 | (-8.4, 3.7) |
| 149-99-03 | 194 | 97.4 | — | — | 388 | 89.7 | -7.7 | (-11.5, -4.0) |

Intent-to-treat population; last observation carried forward (LOCF)
[1] 95% two-sided confidence intervals for the between-group difference in proportions
Source: Table 10-1, pg 95, Vol 1.77, Table 9-1, pg 234, Vol 1.44, and Table 9-1, pg 75, Vol 1.60.

Medical Officer's Comments

- **Based on the agreed upon criteria for achievement and maintenance of suppression of serum testosterone levels, abarelix was not inferior to either of the active treatments in the 2 pivotal trials. The lower bound of the 95% CI was –11.5% in Study 149-99-03 (a supportive study). This observation, per se, is not worrisome since it is only slightly beyond the agreed upon lower limit of –10%, and the success rate for Lupron in this study (97.4%) was extremely high.**

### 8.4.3 Secondary (Supportive) Efficacy Analyses and Endpoints

#### 8.4.3.1 Achievement and Maintenance of Medication Castration From Day 29 Through Day 169 (Assessed by Protocol Definition 5)

Testosterone data obtained in Studies 149-98-02 and 149-98-03 also were analyzed by the Sponsor for achievement and maintenance of medical castration from Study Day 29 through Study Day 169 in accordance with Protocol Definition No. 5 (Table 12). In Study 149-98-02, medical castration was achieved by Day 29 and maintained through Day 169 by 92.1% of the ITT patients in the Lupron group and 87.2% of patients in the abarelix group. In Study 149-98-03, medical castration was achieved by Day 29 and maintained through Day 169 by 84.3% of the patients in the Lupron plus Casodex group and 90.5% of the patients in the abarelix group. The point estimates of the differences between successful achievement and maintenance of medical castration were 4.9% better in the Lupron arm in Study 149-98-02 and 6.1% better in the abarelix arm in Study 149-98-03. The lower bounds of the two-sided 95% confidence intervals for the difference in achievement and maintenance of medical castration were –12.3% in Study 149-98-02 and –2.9% in Study 149-98-03.

Medical Officer's Comments

- **In this secondary analysis, one of the 2 studies (Study 149-98-03) fully supports the Sponsor's claim that treatment with abarelix is not inferior to a GnRH superactive analog in terms of achieving medical castration within 29 days of the onset of treatment and maintaining medical castration through Day 169. The lower bound of –12.3% for the 95% CI for the difference between treatment groups in Study 149-98-02, however, is slightly below –10.0%.**
- **All patients who were withdrawn from the clinical trial because of an adverse event were classified as a treatment failure by the Sponsor. The higher withdrawal rate for adverse events in the Lupron plus Casodex arm of Study 149-98-03, and not better maintenance of testosterone suppression in the abarelix arm, is the primary basis for the difference of 6.1% in favor of the abarelix group.**

- **It also should be noted that a treatment failure (in accordance with Protocol Definition No. 5, a definition analogous to Protocol Definition No. 2 [see Section 8.1.2.1]) requires 2 successive serum testosterone values > 50 ng/dL. If other, more rigorous definitions of success are used to analyze the serum testosterone data through Day 169 (i.e., definitions 4 or 6), the percentage of patients who meet the definition of success is numerically greater in both the Lupron group and the Lupron plus Casodex group compared to the respective abarelix treatment groups (see Section 8.4.3.2).**

**Table 12. Percentage of Patients Who Achieved and Maintained Medical Castration From Day 29 Through Day 169 (No Two Consecutive Testosterone Values > 50 ng/dL)**

| | Treatment Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron | | Lupron plus Casodex | | Abarelix | | Percent Difference | |
| Study | N | Percent | N | Percent | N | Percent | Value | 95% CI[1] |
| 149-98-02 | 89 | 92.1 | — | — | 180 | 87.2 | -4.9 | (-12.3, 2.5) |
| 149-98-03 | — | — | 83 | 84.3 | 168 | 90.5 | 6.1 | ( -2.9, 15.1) |

Intent-to-treat population; last observation carried forward.
[1] 95% two-sided confidence intervals for the between-group difference in proportions.
Source: Table 9-4 in the 149-98-02 and 149-98-03 clinical study reports.

### 8.4.3.2 Achievement and Maintenance of Castration From Day 29 Through Day 169 (Assessed by Other Definitions of Success)

The Sponsor provided supplemental calculations for "achievement and maintenance of medical castration" by secondary definitions of success that were more rigorous than primary Definitions 2 and 5 that were used in Sections 8.4.2.3 and 8.4.3.1, respectively. A successful outcome by these alternative definitions required that (a) all serum testosterone values were ≤ 50 ng/dL (Definitions 1 and 4) or (b) that all testosterone values at the end of each 28-day treatment period were ≤ 50 ng/dL (Definitions 3 and 6). See Section 8.1.2.1 for a complete description of these alternative definitions. For these secondary analyses, the Sponsor elected to use the per protocol population and Kaplan-Meier estimates of the cumulative probability of success rather than the ITT population and simple proportions with the LOCF.

Table 13 summarizes the cumulative probability of achieving and maintaining medical castration using the criteria of no serum testosterone value > 50 ng/dL (Definitions 1 and 4). By these definitions, the cumulative probability of success was numerically lower in the abarelix groups in each of the 3 studies. The largest difference in the cumulative probability of achieving a successful outcome was –15.2% (95% CI: -21.38, -9.03) in Study 149-99-03 for the interval from Day 29 through Day 169.

**Table 13. Cumulative Probability of Achieving and Maintaining Medical Castration (No Serum Testosterone Value > 50 ng/dL – Definitions 1 and 4)**

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | Lupron | Lupron + Casodex | Abarelix | Difference | |
| Study | Cumulative Probability (%) | | | Value | 95% CI |
| *Day 29 through Day 85* | | | | | |
| 149-98-02 | 89.4 | | 83.1 | -6.3 | (-14.91, 2.32) |
| 149-98-03 | | 90.0 | 88.9 | -1.2 | ( -9.35, 6.96) |
| 149-99-03 | 95.7 | | 83.0 | -12.7 | (-17.59, -7.90) |
| *Day 29 through Day 169* | | | | | |
| 149-98-02 | 85.6 | | 74.7 | -11.0 | (-21.04, -0.90) |
| 149-98-03 | | 83.0 | 82.8 | -0.3 | (-10.59, 10.07) |
| 149-99-03 | 90.9 | | 75.7 | -15.2 | (-21.38, -9.03) |

PP Population.

Source: Table 12.4.1.3, pg 296, Vol 1.44, Table 12.4.1.3, pg 143, Vol 1.60, and Table 12.4.1.2, pg 119, Vol 1.77.

Table 14 summarizes the cumulative probability of achieving and maintaining medical castration using the criteria of no serum testosterone value > 50 ng/dL at the end of each 28-day treatment period (Definitions 3 and 6). By these definitions, the cumulative probability of success also was numerically lower in the abarelix groups in each of the 3 studies. The largest difference in the cumulative probability of achieving a successful outcome was –15.6% (95% CI: -21.69, -9.49) in Study 149-99-03 for the interval from Day 29 through Day 169.

**Table 14. Cumulative Probability of Achieving and Maintaining Medical Castration (No Testosterone Value > 50 ng/dL at End of Each Monthly Treatment Course)**

| | Treatment Group | | | | |
|---|---|---|---|---|---|
| | Lupron | Lupron + Casodex | Abarelix | Difference | |
| Study | Cumulative Probability (%) | | | Value | 95% CI |
| *Day 29 through Day 85* | | | | | |
| 149-98-02 | 95.3 | | 84.3 | -11.0 | (-18.11, -3.99) |
| 149-98-03 | | 95.1 | 90.0 | -5.1 | (-11.67, 1.49) |
| 149-99-03 | 95.7 | | 84.0 | -11.6 | (-16.42, -6.87) |
| *Day 29 through Day 169* | | | | | |
| 149-98-02 | 88.8 | | 76.4 | -12.4 | (-21.86, -2.88) |
| 149-98-03 | | 85.3 | 83.9 | -1.4 | (-11.67, 8.48) |
| 149-99-03 | 91.5 | | 75.9 | -15.6 | (-21.69, -9.49) |

PP Population.

Source: Table 12.4.1.3, pg 296, Vol 1.44, Table 12.4.1.3, pg 143, Vol 1.60, and Table 12.4.1.2, pg 119, Vol 1.77.

**Medical Officer's Comments**

- **A successful outcome is more difficult to achieve by the criteria of these alternative definitions in that a patient is considered a treatment failure if only a single (and not 2 consecutive) serum testosterone value is > 50 ng/dL. Assessed by these more rigorous definitions, abarelix was statistically inferior to Lupron in Studies 149-98-02 and 149-99-03.**

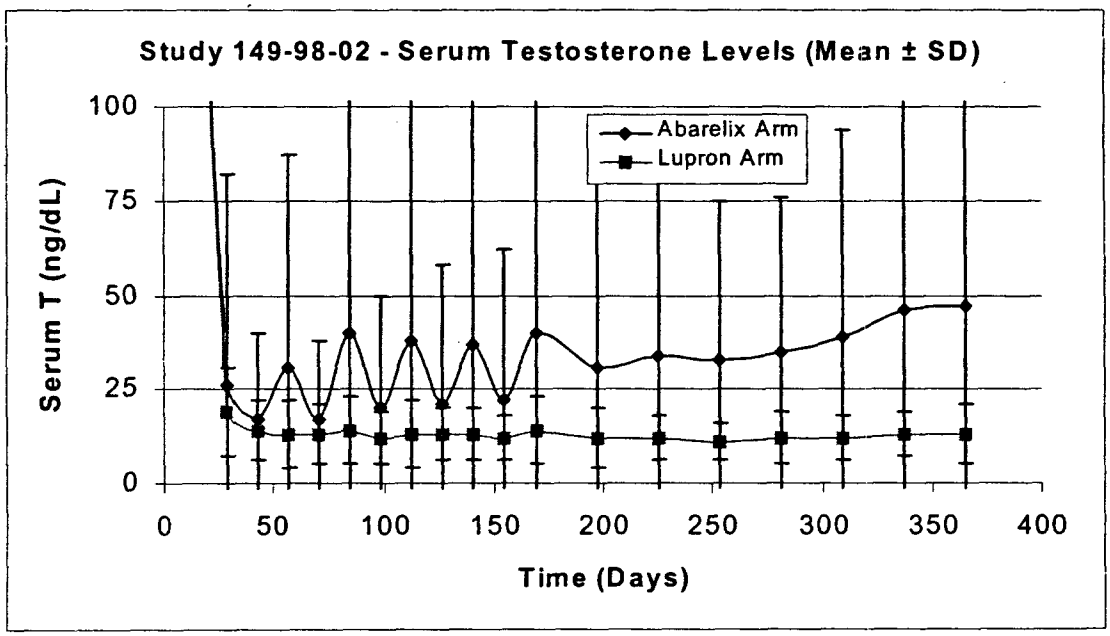
#### 8.4.3.3 Mean Serum Testosterone and Percentage of Patients with Serum Testosterone ≤ 50 ng/dL

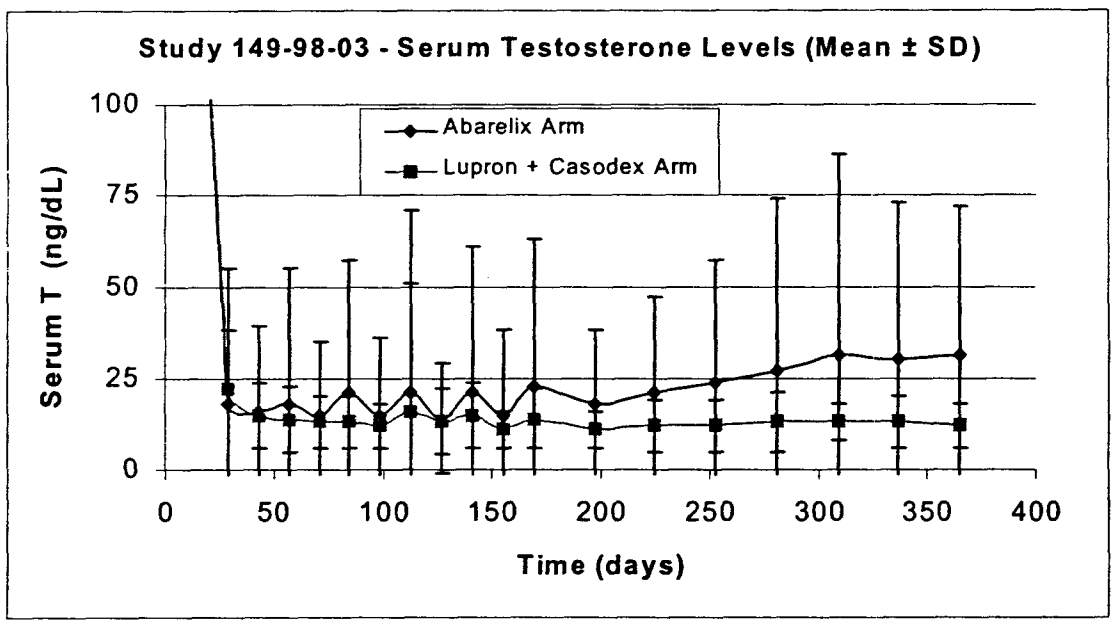
The sponsor did not present in the main body of the Study Reports information on either the mean serum testosterone levels during treatment or the percentages of patients who were medically castrate (serum testosterone ≤ 50 ng/dL) at each protocol defined assessment time after Study Day 29. Such information, however, was available in Data Listings provided in the respective Study Reports.

Mean (±SD) serum testosterone concentrations at each protocol-defined assessment time from Day 29 through Day 365 (end of study participation) are graphically represented for Studies 149-98-02 and 149-98-03 in Figure 4. Serum testosterone measurements were obtained at least once every 14 days through Study Day 169 and once every 28 days (immediately prior to dosing) thereafter. In both Studies 149-98-02 and 149-98-03, mean serum testosterone concentrations were generally numerically higher in the abarelix groups compared to the respective active control group. The difference in mean serum testosterone values was most apparent in samples obtained just prior to dosing, particularly after Study Day 169. The standard error associated with each assessment time was greater in the abarelix treatment groups, a reflection of the variability in serum testosterone values in the abarelix groups.

The percentages of patients with a serum testosterone ≤ 50 ng/dL (i.e., medically castrate) at each assessment time from Day 29 through Day 365 (end of study participation) are graphically represented for Studies 149-98-02 and 149-98-03 in Figure 5. Assessments were obtained at least once every 14 days through Study Day 169 and once every 28 days (immediately prior to dosing) thereafter. In both Study 149-98-02 and 149-98-03, nearly 100% of patients in the active control groups had serum testosterone concentrations of ≤ 50 ng/dL at each assessment. The percentage of patients with serum testosterone values ≤ 50 ng/dL in the abarelix groups was numerically lower than that in the active control groups at most assessments. Eighty percent (80%) or less of the patients in Study 149-98-02 had serum testosterone values of ≤ 50 ng/dL (i.e., were medically castrate) at each monthly assessment from Study Day 253 onward.

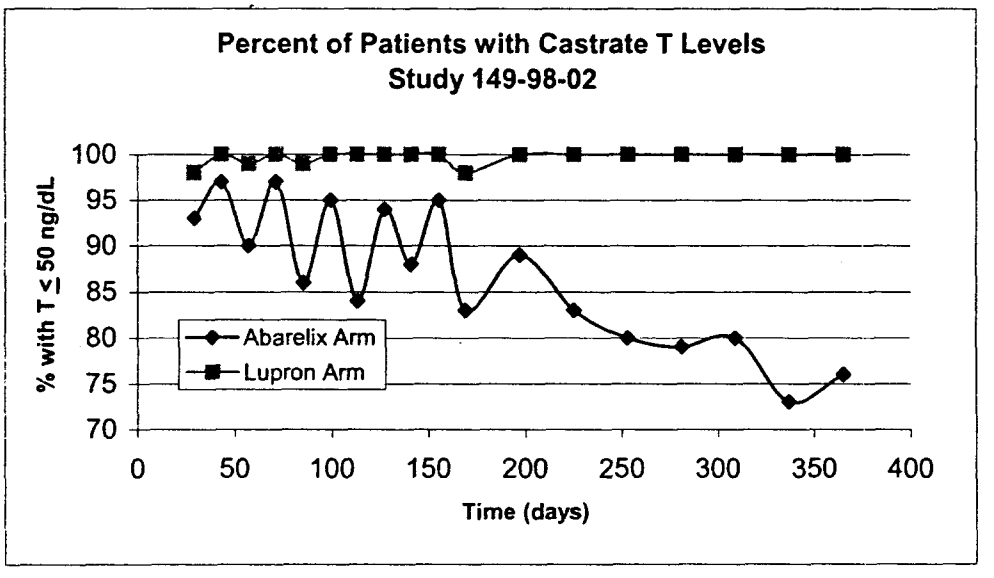
**Figure 4. Mean (±SD) Serum Testosterone Concentrations (Studies 149-98-02 and 149-98-03)**

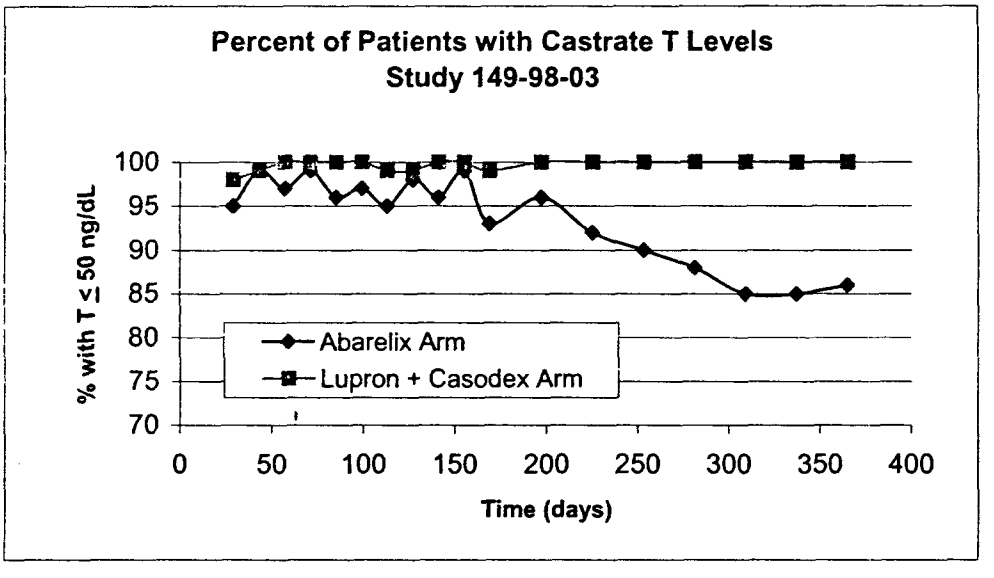



Source: .Table 12.5.7, pg. 87, Vol. 1.52 and Table 12.5.7, pg. 92, Vol. 1.67.

**Figure 5. Percent Of Patients with Serum Testosterone ≤ 50 ng/dL (Medically Castrate)**




Source: Table 12.4.4, pg. 84, Vol. 1.52 and Table 12.4.4, pg. 89, Vol. 1.67

Medical Officer's Comments

- **The descriptive analyses presented in Figures 4 and 5 strongly suggest that abarelix suppresses serum testosterone levels to a lesser extent and less reliably than Lupron or Lupron plus Casodex. This difference is most apparent in assessments made just prior to each dosing with Study Drug (i.e., 28 days after the prior dosing), particularly after Study day 169.**
- **The difference between abarelix and Lupron in terms of suppression of testosterone might be reduced or eliminated by administering a monthly dose of abarelix greater than 100 mg, administering abarelix more frequently (e.g. every 3 weeks), or modifying the formulation so that a greater percentage of the administered dose is released during the latter part of each 28-day dosing cycle.**
- **The analyses presented in Figure 5 are probably of most relevance to the clinical management of patients with prostate cancer since they provide information about the adequacy of testosterone suppression for all patients while they are receiving treatment with abarelix. These data indicate that monitoring of serum testosterone levels would be advisable (and probably necessary) for patients receiving abarelix under the dosing regimen employed in Studies 149-98-02 and 149-98-03.**
- **It is not known if this difference in degree and reliability of suppresses of serum testosterone is clinically important. It is possible that the long-term clinical outcome may be comparable in men with a lesser degree of testosterone suppression (i.e., testosterone values ≤ 75 ng/dL instead of ≤ 50 ng/dL) as observed in the abarelix groups. However, in the absence of such data, one needs to assume that failure to reliably suppress serum testosterone values to those observed in men following surgical castration may have an adverse effect on long term clinical outcomes.**

#### 8.4.3.4 Changes in Serum Concentrations of Pituitary Gonadotropins

Median serum concentrations of LH and FSH in Studies 149-98-02 and 149-98-03 through Study Day 169 are presented in Table 15 and Table 16, respectively. Median serum concentrations of LH and FSH increased 2 to 5 fold after administration of Lupron with maximal values observed on Day 2. Thereafter median values for both LH and FSH declined, with maximal suppression observed by Day 15 for FSH and Day 29 for LH. In contrast, there was no increase in median serum concentrations of LH or FSH following administration of abarelix. In the abarelix groups. median serum LH concentrations were suppressed to 1 IU/L (the limit of assay sensitivity) by Day 2. Median serum concentrations of FSH declined more slowly, reaching lowest values by Study Day 29.

Medical Officer's Comments

- **Although median LH values were reduced to 1 IU/L by Study Day 2 in the abarelix groups, the decline in serum testosterone values was more gradual. Serum testosterone levels were reduced to ≤ 50 ng/dL in only approximately 24% and 70 % of patients by Study Days 2 and 8, respectively (see Table 10).**
- **Abarelix suppresses serum FSH to a greater degree (median nadir values of 1-2 IU/L) than does Lupron (median nadir values of 5 IU/L). The significance of this difference in terms of potential clinical benefit to patients is not known.**

**Table 15 Median Serum Luteinizing Hormone (LH) Levels**

| | Study 149-98-02 | | | | Study 149-98-03 | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron N = 89 | | Abarelix N = 180 | | Lupron + Casodex N = 83 | | Abarelix N = 168 | |
| | n | Median (IU/L) | N | Median[1] (IU/L) | n | Median (IU/L) | n | Median (IU/L) |
| Baseline | 88 | 7 | 180 | 6 | 83 | 6 | 168 | 6 |
| Day 2 | 88 | 30 | 179 | 1 | 80 | 33 | 166 | 1 |
| Day 4 | 85 | 14 | 173 | 1 | 80 | 13 | 162 | 1 |
| Day 8 | 82 | 7 | 177 | 1 | 79 | 6 | 164 | 1 |
| Day 15 | 88 | 2 | 179 | 1 | 79 | 2 | 167 | 1 |
| Day 29 | 88 | 1 | 179 | 1 | 81 | 1 | 168 | 1 |
| Day 57 | 85 | 1 | 174 | 1 | 78 | 1 | 165 | 1 |
| Day 85 | 86 | 1 | 175 | 1 | 80 | 1 | 164 | 1 |
| Day 113 | 84 | 1 | 171 | 1 | 76 | 1 | 161 | 1 |
| Day 141 | 82 | 1 | 169 | 1 | 70 | 1 | 157 | 1 |
| Day 169 | 81 | 1 | 166 | 1 | 69 | 1 | 156 | 1 |

Intent-to-treat population
[1] The lower limit of detection of the assay was 1 IU/L; values below the detection limit are reported as 1 IU/L.
Source: Tables 12.5.9 in the 149-98-02 and 149-98-03 clinical study reports.

**Table 16. Median Serum Follicle-Stimulating Hormone (FSH) Levels**

| | Study 149-98-02 | | | | Study 149-98-03 | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron N = 89 | | Abarelix N = 180 | | Lupron + Casodex N = 83 | | Abarelix N = 168 | |
| | n | Median (IU/L) | n | Median[1] (IU/L) | n | Median (IU/L) | n | Median (IU/L) |
| Baseline | 88 | 9 | 180 | 8 | 83 | 8 | 168 | 8 |
| Day 2 | 88 | 21 | 179 | 5 | 80 | 17 | 166 | 5 |
| Day 4 | 85 | 10 | 173 | 3 | 80 | 9 | 162 | 4 |
| Day 8 | 82 | 4 | 177 | 3 | 79 | 4 | 164 | 3 |
| Day 15 | 88 | 3 | 179 | 2 | 79 | 3 | 167 | 2 |
| Day 29 | 88 | 3 | 179 | 1 | 81 | 3 | 168 | 1 |
| Day 57 | 85 | 4 | 174 | 1 | 78 | 4 | 165 | 1 |
| Day 85 | 86 | 5 | 175 | 2 | 80 | 5 | 164 | 1 |
| Day 113 | 84 | 5 | 171 | 2 | 76 | 5 | 161 | 1 |
| Day 141 | 82 | 5 | 169 | 2 | 70 | 5 | 157 | 1 |
| Day 169 | 81 | 5 | 166 | 2 | 69 | 5 | 156 | 2 |

Intent-to-treat population
[1] The lower limit of detection of the assay was 1 IU/L; values below the detection limit are reported as 1 IU/L.
Source: Tables 12.5.10 in the 149-98-02 and 149-98-03 clinical study reports.

#### 8.4.3.5 Changes in Serum Concentrations of Prostate Specific Antigen (PSA)

Table 17 lists the median percentage changes from baseline for prostate specific antigen (PSA). Serum PSA levels declined significantly from baseline in all treatment groups. In Study 149-98-02, these decreases were numerically greater in the abarelix group on Days 15 and 29 compared to those observed in the Lupron group. In Study 149-98-03, the rate of PSA decrease tended to be greater in the Lupron plus Casodex group. Median serum PSA levels decreased by more than 90% in all treatment groups by Day 85.

**Table 17. Median Percent Change From Baseline in Serum PSA**

| | Study 149-98-02 | | | | Study 149-98-03 | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron N = 89 | | Abarelix N = 180 | | Lupron + Casodex N = 83 | | Abarelix N = 168 | |
| | n | Median % change | n | Median % change | n | Median % change | N | Median % change |
| Day 15 | 86 | -15.0 | 173 | -50.0 | 76 | -45.6 | 161 | -48.5 |
| Day 29 | 85 | -60.9 | 175 | -75.4 | 78 | -81.4 | 163 | -74.5 |
| Day 57 | 84 | -87.1 | 168 | -89.9 | 75 | -96.3 | 160 | -89.1 |
| Day 85 | 80 | -92.6 | 166 | -91.7 | 71 | -97.8 | 150 | -92.3 |
| Day 113 | 77 | -93.8 | 158 | -92.9 | 65 | -98.3 | 148 | -93.4 |
| Day 141 | 73 | -95.8 | 155 | -94.8 | 64 | -98.4 | 146 | -94.7 |
| Day 169 | 70 | -97.2 | 153 | -95.9 | 58 | -98.5 | 140 | -95.8 |

Per-protocol population
Source: Table 12.5.11.2 in the 149-98-02 and 149-98-03 clinical study reports.

Medical Officer's Comment

- **Prostate specific antigen is an indicator of the activity of prostate epithelial cells and is used as a clinical biomarker in the management of men with prostate cancer. Median serum PSA levels were significantly reduced during the first 6 months of treatment in all groups.**

## 8.5 Conclusions Regarding Demonstrated Efficacy

### 8.5.1 Achievement of Protocol-Defined Primary Efficacy Endpoints

The abarelix treatment groups in the 2 principal efficacy studies successfully achieved each of the protocol-defined primary efficacy endpoints. The principal efficacy studies demonstrated that treatment with abarelix, compared to treatment with Lupron alone (Study 149-98-02) or Lupron plus Casodex (Study 149-98-03), resulted in the following:

1. **Avoidance of a testosterone surge**

   No patients in the abarelix treatment groups experienced a testosterone surge while 82% (Study 149-98-02) and 86% (Study 149-98-03) of patients in the active control groups experienced a testosterone surge ($p < 0.001$).

2. **More rapid attainment of medical castration**

   No patients in the active control groups were medically castrate on Day 8 compared with 72% (Study 149-98-02) and 68% (Study 149-98-03) of the abarelix-treated patients ($p < 0.001$).

3. **Comparable proportion of patients achieving and maintaining medical castration from Day 29 through Day 85 (no two consecutive testosterone values > 50 ng/dL)**

Medical castration was achieved and maintained by 95.5% and 95.2% of the active control patients and 91.7% and 92.9% of the abarelix patients, respectively, in Studies 149-98-02 and 149-98-03. By prior agreement, treatment with abarelix was declared to be noninferior to that of Lupron or Lupron plus Casodex since the lower bound of the 95% CI for the differences between the treatment groups was not less than –10%. The lower bound of the 95% CI for supportive Study 149-99-03 was slightly below the limit of –10%.

| | Treatment Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lupron | | Lupron plus Casodex | | Abarelix | | Percent Difference | |
| | N[1] | Percent[2] | N | Percent | N | Percent | Value | 95% CI |
| 149-98-02 | 89 | 95.5 | — | — | 180 | 91.7 | -3.8 | (-9.7, 2.1) |
| 149-98-03 | — | — | 83 | 95.2 | 168 | 92.9 | -2.3 | (-8.4, 3.7) |
| 149-99-03 | 194 | 97.4 | — | — | 388 | 89.6 | -7.7 | (-11.5, -4.0) |

[1] Number patients in the ITT population.
[2] Percentage of patients who achieved and maintained testosterone suppression.
Source: Table 10-1, pg 95, Vol 1.77, Table 9-1, pg 234, Vol 1.44, and Table 9-1, pg 75, Vol 1.60.

### 8.5.2 Support of Label Efficacy Claim

The sponsor's label claim that treatment with abarelix is (a) not associated with an initial surge of testosterone and (b) suppresses serum testosterone levels more rapidly than a superactive GnRH agonist (i.e. Lupron) is fully supported by the clinical data. The sponsor's claim

will need to be clarified by including the definition of success (i.e., no two consecutive testosterone values >50 ng/dL). By alternative definitions of success (all of which have more clinical relevance in the opinion of this reviewer), abarelix was not noninferior to Lupron in one of the 2 primary efficacy studies (Study 149-98-02) and the supportive efficacy study (Study 149-99-03) in terms of maintaining testosterone suppression through Day 85 as the lower bound of the 95% CI was less than –10% (see Table 13 and Table 14). The label also will need to include information indicating that (a) abarelix appeared to be less effective than Lupron in maintaining testosterone suppression to ≤ 50 ng/dL after Day 169 and (b) guidance to physicians regarding the importance of monitoring the serum testosterone levels in men treated with abarelix. See Section 8.8 for a further discussion of this issue.

## 8.6 Supportive Efficacy Study 149-98-04

This was an uncontrolled, multicenter study in men with advanced metastatic prostate. These patients, for the most part, had symptoms or physical findings that strongly suggested that treatment with a superactive GnRH agonist, without concomitant antiandrogen therapy, might result in a clinically significant exacerbation of their symptoms or a medically serious complication. The sponsor felt that treatment of these men with a GnRH agonist was contraindicated. The primary objective of the Study was to determine if these patients could be treated safely with abarelix and could thus avoid bilateral orchiectomy. Eighty one (81) men were enrolled and treated with abarelix in Study 149-98-04.. Entry criteria for this Study required that patients have 1 of the following 4 conditions: bone pain from skeletal metastases, bilateral retroperitoneal adenopathy causing ureteral obstruction, impending neurological compromise, or the presence of an enlarged prostate gland or pelvic mass causing bladder neck outlet obstruction. Serum testosterone was reduced to ≤ 50 ng/dL in 30% and 79% of the patients by treatment Day 2 and Day 8, respectively. All of the patients avoided orchiectomy, demonstrating that abarelix could be administered to these high risk patients

without a serious exacerbation in their symptoms of prostate cancer. It is not known, however, what percentage of these patients would have had a testosterone surge of sufficient magnitude to necessitate an orchiectomy had they been treated with a superactive GnRH agonist alone or in combination with an antiandrogen. The executive summary of the review of Study 149-99-04 conducted by Dr. G Benson, Medical Officer, DRUDP, is included as Appendix A.

## 8.7 Statistician's Assessment of Efficacy (Protocol-Defined Primary Endpoints)

The validity of the sponsor's analyses in support of the primary efficacy endpoints was confirmed by the FDA statistician. See the separate Statistical Review for further information.

## 8.8 Medical Officer's Overall Assessment of Efficacy (Statistical and Clinical Significance)

The sponsor has demonstrated with high statistical probability that treatment with abarelix suppresses serum testosterone levels more rapidity than does treatment with Lupron (a superactive GnRH agonist) and does so without initially producing a testosterone surge. Both of these aspects of treatment with abarelix are of clinical benefit, particularly the absence of a testosterone surge in certain high risk patients such as those that were enrolled in Study 149-98-04. Based on criteria agreed to by both the Sponsor and DRUDP for achievement and maintenance of suppression of serum testosterone levels (Protocol Definition No. 2), abarelix also was found to be noninferior to either of the active treatments in the 2 pivotal efficacy trials.

Failure to maintain suppression, based on Protocol Efficacy Definition No. 2, required that serum testosterone levels in 2 successive blood samples taken 2 weeks apart be > 50 ng/dL. This liberal definition thus did not classify a patient who had a serum testosterone > 50 ng/dL at the end of each 28-day dosing cycle as a treatment failure. This situation occurred more frequently with abarelix treatment than with Lupron treatment. If maintenance of testosterone suppression was assessed by more rigorous criteria (i.e. no testosterone values >50 ng/dL or no predosing values > 50 ng/dL), abarelix was not noninferior (i.e., was not equivalent) to Lupron over the period from Day 29-85 and was somewhat inferior to Lupron over the period from Days 29-169 (see Table 13 and Table 14).

The descriptive analyses presented in Figure 4 and Figure 5 also strongly suggest that abarelix is not as effective as Lupron or Lupron plus Casodex in reliably maintaining testosterone suppression to ≤ 50 ng/dL, especially after treatment Day 169. These data indicate that some monitoring of serum testosterone levels would be necessary for patients receiving long term treatment abarelix under the dosing regimen employed in Studies 149-98-02 and 149-98-03. These differences between abarelix and Lupron in terms of long term reliability of testosterone suppression will be addressed in the label for abarelix. It is not known, however, if the differences in degree and reliability of suppresses of serum testosterone seen in Studies 149-98-02 and 149-98-03 are clinically important. It is possible that the long-term clinical outcome may be comparable in men with a lesser degree of testosterone suppression as observed in the abarelix groups. However, in the absence of such clinical data, one needs to assume that failure to reliably suppress serum testosterone values to those observed in men following surgical castration may have an adverse effect on long term clinical outcomes.

# 9 INTEGRATED REVIEW OF SAFETY

## 9.1 Safety Studies

Data from 12 clinical studies were submitted by the Sponsor to support the safety of abarelix depot. Figure 1 (Section 6.2) provides an overview of these studies and includes the study identifier and the number of patients assigned to each treatment group in each study. Five of these 12 studies were conducted either in (a) women with endometriosis (Studies 149-98-05 and 149-99-02), (b) men with prostate cancer using an injectable solution formulation of abarelix administered by continuous SC infusion and not the to be marketed [redacted] formulation (Studies 149-96-01 and 149-97-03), or (c) normal male volunteers (Study 149-99-01, a pharmacokinetic study). According to the sponsor, there were no safety findings from these studies that would impact on the overall safety assessment of abarelix depot for the indication of palliative management of prostate cancer. In these 5 studies, there were no reports of death, serious systemic allergic reactions, or significant hepatotoxicity. Consequently, these studies were not reviewed further. The remaining 7 clinical studies were conducted in men with prostate cancer using the depot formulation of abarelix. Details about each of these 7 Studies are provided in Section 6.2 and Table 2 of this review. Three of these 7 studies were controlled, randomized studies that were sponsored by Praecis (the Sponsor of this IND). They were identified by the Sponsor as the "principal safety studies."

- 149-98-02 "A Phase III, Multi-Center, Open-Label, Randomized Study of Abarelix-Depot vs. Lupron® Depot 1-Month in Patients With Prostate Cancer Who Are Candidates for Initial Hormonal Therapy"
- 149-98-03 "A Phase III, Multi-Center, Open-Label, Randomized Study of Abarelix-Depot vs. Lupron® Depot 1-Month Plus Daily Casodex® in Patients With Prostate Cancer Who Are Candidates for Initial Hormonal Therapy"
- 149-99-03 "A Phase 3, Multicenter, Open-Label, Randomized Study of Abarelix-Depot 100 mg IM vs Lupron Depot® 7.5 mg IM in Patients With Prostate Cancer Who Are Candidates for Initial Hormonal Therapy"

Each of these Phase III studies required that patients undergo at least 6 months of treatment (through Study Day 169). Patients randomized to the abarelix groups received a 100-mg IM injection on Days 1, 15, and 29, and every 28 days thereafter. Patients enrolled in Study 149-98-02 and Study 149 98 03 had the option to continue treatment for up to 1 year. After 1 year, those patients receiving abarelix could continue treatment in rollover Study 149-99-04. Patients receiving treatment with abarelix in Study 149-99-03 (a study of only 6 months duration) also could continue treatment with abarelix in rollover Study 149-99-04.

### 9.1.1 Exposure to Abarelix Depot

A total of 1166 prostate cancer patients were exposed to abarelix depot (Table 18). Of the 1166 patients, 834 patients received the proposed registration dose of abarelix ( 100 mg for both induction [initial 1 or 2 doses] and maintenance of medical castration). A total of 752 of these patients were exposed to the proposed registration dose of abarelix for at least 6 months, and 190 patients were exposed for at least 1 year.

**Table 18. Number of Patients Exposure to Abarelix Depot**

| | Any Exposure n | 6 Months Exposure [1] n | 1 Year Exposure [2] n |
|---|---|---|---|
| **Studies with 100 mg Dose of Abarelix (Proposed Registration Dosing Regimen)** | | | |
| *Principal Safety Studies* | | | |
| 149-98-02 | 180 | 170 | 94 |
| 149-98-03 | 168 | 157 | 89 |
| 149-99-03 | 387 | 345 | 0 |
| Subtotal | 735 | 672 | 183 |
| *Supportive Safety Studies* | | | |
| 149-98-04 | 81 | 70 | 2 |
| 149-97-04 | 18 | 10 | 5 |
| Subtotal | 99 | 80 | 7 |
| **Total** | **834** | **752** | **190** |
| **Non-Registration Dosing Regimens or non-Praecis Sponsored Studies** | | | |
| 149-97-04 | 245 | | |
| ABACAS 1 | 87 | | |
| **Total** | **332** | | |
| **Any Exposure to 100 mg Dose of Abarelix Depot** | | | |
| **Grand total** | **1166** | **> 752** | **≥ 190** |

[1] Received Day 141 dose; exposure defined as continuing for 28 days after the final dose of abarelix.
[2] Received Day 337 dose; exposure defined as continuing for 28 days after the final dose of abarelix.
Source: Safety Update (submitted 13 March 2001), Table 10 A, pg 122.

Medical Officer's Comment.

- **Studies 149-98-02, 149-98-03, and 149-99-03 were the most valuable studies for assessing the overall safety of abarelix relative to that of presently used hormonal therapy for the management of prostate cancer (i.e., superactive GnRH agonists). These studies were considered to be the principal safety studies, both by the Sponsor and by this reviewer, and were the focus of this safety review. The remaining 4 studies conducted with abarelix depot in men with prostate cancer were reviewed primarily for areas of particular safety concern, namely, allergic reactions and potential liver toxicity, as well as for deaths and other serious adverse events.**

## 9.2 Protocol Defined Safety Assessments in Primary Safety Studies

Important safety assessments included treatment-emergent adverse events, laboratory abnormalities, and development of anti-abarelix antibodies. Table 5 lists the schedule of protocol-required safety assessments.

### 9.2.1 Adverse Events

Adverse events were recorded and monitored throughout the clinical trials. The World Health Organization (WHO) Toxicity Scale was used, whenever possible, to rate the severity of adverse events. An endocrine questionnaire was used to record reports of adverse events likely to be a result of decreased androgen levels. Signs and symptoms recorded on the endocrine questionnaire were considered to be adverse events, as were abnormal hematology and clinical chemistry test results, but neither the endocrine questionnaire symptoms nor laboratory abnormalities were normally recorded as adverse events on the adverse event case report form (CRF).

Because disease progression was assessed as an efficacy endpoint, it was not considered to be an adverse event. Any preplanned hospitalization for elective procedures, or hospitalization for prostatectomy, was not considered to be a serious adverse event.

### 9.2.2 Clinical Laboratory Tests

Laboratory evaluations were performed at screening, at baseline, at 4-week intervals during treatment, at end-of-treatment, and at the 4-week posttreatment follow-up visit. The following hematology and clinical chemistry assessments were performed:

| | |
|---|---|
| Hematology | Complete blood count: red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, reticulocyte count, white blood cell (WBC) count |
| | Differential: Neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils, basophils |
| Clinical chemistry | Electrolytes and other constituents: sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium |
| | Liver function tests: alkaline phosphatase, ALT, AST, total bilirubin |
| | Renal function and other tests: glucose, hemoglobin $A_{1c}$, blood urea nitrogen (BUN), creatinine, total protein, albumin, creatine kinase |
| | Lipids: triglycerides, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL). Fasting samples were to be collected at study visits on Days 1, 85, 169, 253, and 337. |

If a patient in the abarelix or Lupron treatment groups experienced an elevated ALT or AST value $\geq 5.1$ x ULN (grade 3 toxicity, WHO toxicity scale), a repeat blood draw was to be performed 3, 7, and 12 days after the date of the abnormality. If there was not a significant improvement in laboratory values during this period, the patient was to be withdrawn. In the Lupron plus Casodex group, ALT or AST values > 2 x ULN were the reference level used to determine if a patient should be withdrawn from treatment.

**Clinically notable laboratory values.** To assist in identifying abnormal laboratory test results of particular concern, the sponsor presented in summary tables "clinically notable laboratory values." These values were defined as follows:

Hemoglobin
< 8.0 g/dL
< 9.5 g/dL
> 19.0 g/dL

Hematocrit
< 24%
> 55%

Platelet count
< 75 x $10^3$/$mm^3$

WBC count
< 2.0 x $10^3$/$mm^3$
> 15.0 x $10^3$/$mm^3$

Sodium
< 125 mEq/L
> 155 mEq/L

Potassium
< 3.0 mEq/L
> 5.8 mEq/L

Bicarbonate
< 15.1 mEq/L
> 34.9 mEq/L

Calcium
< 7.0 mg/dL
> 11.0 mg/dL

Magnesium
< 0.5 mEq/L
> 3.0 mEq/L

Alkaline phosphatase
> 200 U/L
> 5.0 x ULN

ALT
> 2.5 x ULN
> 200 U/L

AST
> 2.5 x ULN
> 200 U/L

Total bilirubin
> 2.5 x ULN

Glucose
< 45 mg/dL
> 300 mg/dL

BUN
> 35 mg/dL
> 2.5 x ULN

Creatinine
> 2.0 mg/dL
> 2.5 x ULN

Creatine kinase
> 1000 U/L

**WHO Toxicity Grades.** In addition to standard shift analyses (e.g., shifts from normal to above the normal range), the Sponsor also provided shift analyses based on WHO toxicity grades for laboratory values of particular importance (e. g., ALT, AST, alkaline phosphatase, and triglycerides). WHO Toxicity Grades are defined in Table 19.

**Table 19. WHO Toxicity Grading Scale**

| | Grade 0 x ULN | Grade 1 x ULN | Grade 2 x ULN | Grade 3 x ULN | Grade 4 x ULN |
|---|---|---|---|---|---|
| AST | ≤ 1.25 | 1.26 - 2.59 | 2.60 - 5.09 | 5.10 - 10.00 | > 10.00 |
| ALT | ≤ 1.25 | 1.26 - 2.59 | 2.60 - 5.09 | 5.10 - 10.00 | > 10.00 |
| Alkaline Phosphatase | ≤ 1.25 | 1.26 - 2.59 | 2.60 - 5.09 | 5.10 - 10.00 | > 10.00 |
| BUN | ≤ 1.25 | 1.26 - 2.59 | 2.60 - 5.09 | 5.10 - 10.00 | > 10.00 |
| Triglycerides | ≤ 1.0 | 1.1 - 1.5 | 1.6 - 2.0 | 2.1 - 2.6 | > 2.6 |
| Cholesterol | ≤ 1.0 | 1.1 - 1.5 | 1.6 - 2.0 | 2.1 - 2.6 | > 2.6 |

### 9.2.3 Anti-abarelix Antibodies

Plasma samples were collected at screening and at Days 85, 169, 253, and 337 and at the follow up visit for testing for anti-abarelix antibodies. Testing was based on an enzyme-linked immunosorbent assay (ELISA) for determination of the titer of anti-abarelix IgG antibodies.

## 9.3 Patient Disposition (Principal Safety Studies)

Of the 1,102 patients enrolled in Studies 149-98-02, 149-98-03, and 149-99-03, 284 patients were treated with Lupron, 83 patients were treated with Lupron plus Casodex, and 735 patients were treated with abarelix (Table 20). Ninety percent (90%) of the Lupron group, 84% of the Lupron plus Casodex group, and 91% of the abarelix group completed participation in their respective studies

through Study Day 169. Four percent (4%) of the Lupron group, 10% of the Lupron plus Casodex group, and 3% of the abarelix group were withdrawn from treatment before Day 169 because of adverse events.

Of the 358 patients who continued treatment beyond Day 169, 62 continued treatment with Lupron, 48 continued treatment with Lupron plus Casodex, and 248 continued treatment with abarelix. Of the patients who continued treatment, 3 of 62 (5%) of the Lupron group, 1 of 48 (2%) of the Lupron plus Casodex group, and 5 of 248 (2%) of the abarelix group were withdrawn from treatment after Day 169 and before Day 365 because of adverse events.

**Table 20. Patient Enrollment and Disposition (Pooled Data from Studies 149-98-02, 149-98-03, and 149-99-03)**

| | Treatment Group | | |
|---|---|---|---|
| | Lupron N = 284 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 735 (n (%) |
| Received Study Drug | 284 (100) | 83 (100) | 735 (100) |
| Terminated Study Before Day 169 | 28 (10) | 13 (16) | 69 ( 9) |
| Death | 0 | 0 | 4 ( 1) |
| Adverse event [1] | 12 ( 4) | 8 (10) | 23 ( 3) |
| Patient decision [2] | 4 ( 1) | 3 ( 4) | 16 ( 2) |
| Protocol violation | 8 ( 3) | 2 ( 2) | 7 ( 1) |
| Lost to follow-up | 1 ( 1) | 0 | 3 ( 1) |
| Other | 3 ( 1) | 0 | 16 ( 2) |
| Completed Study Through Day 169 | 256 (90) | 70 (84) | 666 (91) |
| Continued Treatment After Day 169 [3] | 62 (100) | 48 (100) | 248 (100) |
| Withdrawn from treatment before Day 365 | 12 (19) | 12 (25) | 43 (17) |
| Death | 1 ( 2) | 0 | 2 ( 1) |
| Adverse event | 3 ( 5) | 1 ( 2) | 5 ( 2) |
| Patient decision | 3 ( 5) | 5 (10) | 15 ( 6) |
| Protocol violation | 0 | 3 ( 6) | 3 ( 1) |
| Other | 5 ( 8) | 3 ( 6) | 18 ( 7) |
| Completed treatment before Day 365 (physician's decision) | 3 ( 5) | 4 ( 8) | 23 ( 9) |
| Completed treatment through Day 365 | 47 (76) | 32 (67) | 182 (73) |

[1] Includes clinical and laboratory adverse events (e.g., transaminase elevations)
[2] Includes voluntary withdrawal and refusal to receive study drug as randomized
[3] Only includes patients in studies 149-98-02 and 149-98-03 since Study 149-99-03 was of 6-months duration.
Source: Table 4-a, ISS.

**Medical Officer's Comment**

- **The percentage of patients who were prematurely withdrawn from the abarelix group for an adverse event was numerically lower or comparable to those for the Lupron or Lupron plus Casodex groups. The overall percentage of patients who died was higher in the abarelix group (0.83%, 6 of 735 patients) compared to the combined Lupron and Lupron plus Casodex groups (0.27%, 1 of 367 patients). None of the deaths was attributed to Study Drugs (see Section 9.6)**

## 9.4 Demographics and Other Baseline Characteristics (Principal Safety Studies)

Pooled demographic and other baseline characteristics for the patients in the 3 principal safety studies are listed in Table 21. Similar data for each of the 3 principal safety studies, presented separately by study, are listed in Table 6 and Table 7. In general, the treatment groups were similar with respect to age (median 72 to 74 yrs), race (predominantly Caucasian), and body weight (69% to 73% of patients < 200 pounds).

**Table 21. Demographics and Other Baseline Characteristics (Pooled Results from Studies 149-98-02, 149-98-03, and 149-99-03)**

| | Treatment Group | | |
|---|---|---|---|
| Characteristic | Lupron N = 284 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 735 n (%) |
| Age (yr) | | | |
| Median (range) | 73 (49 - 89) | 74 (49 - 93) | 72 (46 – 97) |
| Race/Ethnicity | | | |
| Caucasian | 233 ( 82) | 69 ( 83) | 619 ( 84) |
| African American | 28 ( 10) | 10 ( 12) | 71 ( 10) |
| Hispanic | 16 ( 6) | 2 ( 2) | 23 ( 3) |
| Asian | 5 ( 2) | 2 ( 2) | 13 ( 2) |
| Other | 2 ( 1) | 0 | 9 ( 1) |
| Body Weight (lb) | | | |
| < 200 | 195 ( 69) | 61 ( 73) | 507 ( 69) |
| ≥ 200 | 89 ( 31) | 22 ( 27) | 228 ( 31) |
| Cancer Stage | | | |
| T1 | 56 ( 20) | 13 ( 16) | 140 ( 19) |
| T2 | 117 ( 41) | 27 ( 33) | 257 ( 35) |
| T3 | 27 ( 10) | 4 ( 5) | 83 ( 11) |
| T4 | 4 ( 1) | 1 ( 1) | 2 (< 1) |
| D0 | 4 ( 1) | 0 | 6 ( 1) |
| D1.5 | 56 ( 20) | 33 ( 40) | 176 ( 24) |
| D1 | 7 ( 2) | 1 ( 1) | 36 ( 5) |
| D2 | 13 ( 5) | 4 ( 5) | 35 ( 5) |
| Reason for Treatment in This Study | | | |
| D1/D2 disease stage[1] | 20 ( 7) | 4 ( 5) | 67 ( 9) |
| Rising PSA | 80 ( 28) | 36 ( 43) | 208 ( 28) |
| Neoadjuvant hormonal therapy | 134 ( 47) | 33 ( 40) | 338 ( 46) |
| Intermittent hormonal therapy | 50 ( 18) | 10 ( 12) | 119 ( 16) |
| None of the above | 0 | 0 | 3 (< 1) |

[1] The number of patients enrolled for treatment of D1/D2 stage disease may be less than the sum of patients with a baseline diagnosis of D1/D2 stage disease because another reason (e.g., rising PSA, neoadjuvant hormonal therapy, or intermittent hormonal therapy) may have been given on the case report form.

Source: Table 4-B, pg 144, ISS.

**Medical Officer's Comment**

- **Overall, the 3 treatment groups appeared to be reasonably well balanced.**
- **A higher percentage of patients in the Lupron plus Casodex group (46%) had Stage D prostate cancer compared to the other groups (Lupron: 28%, abarelix 34%).**

## 9.5 Adverse Events

**Medical Officer's Comment**

In this review, adverse events for the principal safety studies (Studies 149-98-02, 149-98-03, and 149-99-03) are presented and discussed in the following manner. An overview of reported adverse events, based on the numbers of patients reporting adverse events summarized into broad categories, is presented (Section 9.5.1). This is followed a summary and discussion of (a) the most commonly reported adverse events (all degrees of severity and all relationships to Study Drugs, Section 9.5.2), (b) the most commonly reported adverse events possibly related to treatment with Study Drugs (Section 9.5.3), (c) treatment-related adverse events that resulted in withdrawal of patients from the clinical trials (Section 9.5.4), (d) severe or life-threatening treatment-related adverse events (Section 9.5.5), and (e) nonfatal, serious treatment-related adverse events (Section 9.5.6). Within each of the first 3 broad classifications (i.e., Sections 9.5.2-9.5.4), adverse events are summarized by (a) those that occurred during the first 169 days following the onset of treatment (based on pooled data from the 3 principal safety studies) and (b) those that occurred in patients with up to 1 year of exposure to Study Drug (limited to Studies 149-98-02 and 149-98-03 since Study 149-99-03 was only of 6-months duration).

Adverse events associated with allergic reactions and transaminase elevations are reviewed separately in Sections 9.9.1 and 9.9.2

### 9.5.1 Overview of Adverse Events (Principal Safety Studies)

Table 22 summarizes the number and type of adverse events reported from Study Day 1 through Day 169 in the 3 principal safety studies. Most patients reported one or more adverse events during this period. For most adverse event categories, the highest percentage of patients reporting an adverse event was in the Lupron plus Casodex group. Withdrawals due to adverse events were highest in the Lupron plus Casodex group (10% of patients). The reported incidences of adverse events in the Lupron and abarelix groups were similar for most categories of adverse events. Four deaths (4 of 735, <1% of patients) were reported in the abarelix group.

**Table 22. Number of Patients Reporting Adverse Events Through Study Day 169 (Pooled Results from Studies 149-98-02, 149-98-03, and 149-99-03)**

| | Lupron N = 284 n (%)[1] | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 735 n (%) |
|---|---|---|---|
| All adverse events | 249 ( 88) | 79 ( 95) | 662 ( 90) |
| Severe or life-threatening | 51 ( 18) | 15 ( 18) | 105 ( 14) |
| Nonfatal serious | 26 ( 9) | 12 ( 14) | 67 ( 9) |
| Treatment-related adverse events | 137 ( 48) | 47 ( 57) | 374 ( 51) |
| Severe or life-threatening | 15 ( 5) | 2 ( 2) | 22 ( 3) |
| Nonfatal serious | 2 ( 1) | 2 ( 2) | 10 ( 1) |
| Withdrawals due to adverse events | 12 ( 4) | 8 ( 10) | 23 ( 3) |
| Deaths on study | 0 | 0 | 4 ( 1) |

Categories are not mutually exclusive.

[1] Number of patients experiencing one or more adverse events in the respective category.

Source: Table 6-A ISS and Table 6-A Safety Update.

Patients in Study 149-98-02 and Study 149-98-03 were allowed to continue treatment for up to 1 year. Adverse events from these studies from Study Day 1 through Day 365 are summarized in Table 23. In general, the percentages of patients reporting at least one adverse event in each of the adverse

event categories were comparable across the 3 treatment groups. However, a higher percentage of patients in the Lupron plus Casodex group (61%) and the abarelix group (52%) reported treatment-related adverse events than in the Lupron group (42%). A higher percentage of patients in the Lupron plus Casodex group (12%) and the Lupron group (9%) were withdrawn from treatment because of an adverse event.

**Table 23. Number of Patients Reporting Adverse Events with Up to 1 Year of Exposure to Study Drug (Pooled Results from Studies 149-98-02 and 149-98-03)**

| | Lupron N = 89 n (%) [1] | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 348 n (%) |
|---|---|---|---|
| All adverse events | 83 (93) | 79 (95) | 335 (96) |
| Severe or life-threatening | 22 (25) | 21 (25) | 73 (21) |
| Nonfatal serious | 17 (19) | 15 (18) | 55 (16) |
| Treatment-related adverse events | 37 (42) | 51 (61) | 181 (52) |
| Severe or life-threatening | 3 ( 3) | 2 ( 2) | 11 ( 3) |
| Nonfatal serious | 1 ( 1) | 2 ( 2) | 7 ( 2) |
| Withdrawals due to adverse events | 8 ( 9) | 10 (12) | 15 ( 4) |
| Deaths on study | 1 ( 1) | 0 | 6 ( 2) |

Categories are not mutually exclusive.
[1] Number of patients experiencing one or more adverse events in the respective category.
Source: Safety Update, Table 6-I, pg 56.

Medical Officer's Comments

- **The percentages of patients represented in Tables 22 and 23 who reported adverse in each of the categories were comparable, for the most part, in the Lupron and abarelix groups. Exceptions included a higher percentage of patients who experienced treated-related adverse events in the abarelix group (Table 23) and a slightly higher percentage of deaths, also in the abarelix group (Tables 22 and 23).**

### 9.5.2 Adverse Events (All Intensities and All Relationships to Study Drug)

All adverse events (regardless of intensity or likely relationship to Study Drug) that occurred through Day 169 in at least 5% of patients treated with abarelix are pooled across studies and listed in Table 24. Adverse events were reported for 249 of 284 (88%) patients in the Lupron group, 79 of 83 (95%) patients in the Lupron plus Casodex group and 662 of 735 (90%) patients in the abarelix group. A similar listing for adverse events that occurred in patients treated for up to 1 year (Studies 149-98-02 and 149-98-03) is presented in Table 25. In patients treated for up to 1 year, adverse events were reported for 83 of 89 (93%) patients in the Lupron group, 79 of 83 (95%) patients in the Lupron plus Casodex group and 335 of 348 (96%) patients in the abarelix group.

**Table 24. Adverse Events (All Treatment Relationships) Occurring Through Day 169 in 5% or More of Patients in the Abarelix Group (Studies 149-98-02, 149-98-03, and 149-99-03)**

| Preferred Term | Lupron N = 284 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 735 n (%) |
|---|---|---|---|
| *Any Adverse Event* | *249 ( 88)* | *79 ( 95)* | *662 ( 90)* |
| Pain | 53 ( 19) | 16 ( 19) | 144 ( 20) |
| Upper resp tract infection | 45 ( 16) | 15 ( 18) | 139 ( 19) |
| Fatigue | 43 ( 15) | 17 ( 20) | 131 ( 18) |
| Micturition frequency | 32 ( 11) | 4 ( 5) | 101 ( 14) |
| Headache | 33 ( 12) | 14 ( 17) | 99 ( 13) |
| Diarrhea | 32 ( 11) | 10 ( 12) | 95 ( 13) |
| Back pain | 23 ( 8) | 13 ( 16) | 66 ( 9) |
| Constipation | 19 ( 7) | 9 ( 11) | 62 ( 8) |
| Dizziness | 19 ( 7) | 9 ( 11) | 61 ( 8) |
| Coughing | 17 ( 6) | 1 ( 1) | 54 ( 7) |
| Nausea | 19 ( 7) | 6 ( 7) | 53 ( 7) |
| Dysuria | 23 ( 8) | 2 ( 2) | 50 ( 7) |
| Rash[1] | 14 ( 5) | 11 ( 13) | 49 ( 7) |
| Rhinitis | 11 ( 4) | 8 ( 10) | 45 ( 6) |
| Abdominal pain | 13 ( 5) | 10 ( 12) | 43 ( 6) |
| Influenza-like symptoms | 14 ( 5) | 3 ( 4) | 43 ( 6) |
| Myalgia | 21 ( 7) | 6 ( 7) | 43 ( 6) |
| Peripheral edema | 20 ( 7) | 9 ( 11) | 39 ( 5) |
| Testis disorder | 13 ( 5) | 3 ( 4) | 38 ( 5) |
| Nocturia | 12 ( 4) | 3 ( 4) | 36 ( 5) |
| Impotence | 16 ( 6) | 2 ( 2) | 35 ( 5) |

Based on descending order of frequency in the abarelix group through Day 169

[1] Includes rash, erythematous rash, maculopapular rash

Source: Table 6-E, ISS, pg 163, Vol 1.108.

**Table 25. Adverse Events (All Treatment Relationships) Occurring in 5% or More of Patients With Up to 1 Year of Exposure to Study Drug (Studies 149-98-02 and 149-98-03)**

| | Treatment Group | | |
|---|---|---|---|
| Preferred Term | Lupron N = 89 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 348 n (%) |
| *Any Adverse Event* | *83 (93)* | *79 (95)* | *335 (96)* |
| Upper resp tract infection | 23 (26) | 22 (27) | 87 (25) |
| Pain | 22 (25) | 21 (25) | 85 (24) |
| Fatigue | 15 (17) | 19 (23) | 63 (18) |
| Diarrhea | 15 (17) | 11 (13) | 59 (17) |
| Micturition frequency | 10 (11) | 7 ( 8) | 52 (15) |
| Headache | 10 (11) | 14 (17) | 51 (15) |
| Back pain | 12 (13) | 14 (17) | 48 (14) |
| Dizziness | 10 (11) | 10 (12) | 45 (13) |
| Constipation | 6 ( 7) | 9 (11) | 32 ( 9) |
| Dysuria | 7 ( 8) | 4 ( 5) | 32 ( 9) |
| Myalgia | 10 (11) | 7 ( 8) | 32 ( 9) |
| Peripheral edema | 19 (21) | 12 (14) | 32 ( 9) |
| Rash[1] | 11 (12) | 14 (17) | 32 ( 9) |
| Influenza-like symptoms | 8 ( 9) | 6 ( 7) | 31 ( 9) |
| Nausea | 7 ( 8) | 6 ( 7) | 30 ( 9) |
| Accidental injury | 3 ( 3) | 4 ( 5) | 29 ( 8) |
| Abdominal pain | 5 ( 6) | 10 (12) | 27 ( 8) |
| Rhinitis | 6 ( 7) | 9 (11) | 27 ( 8) |
| Surgical intervention | 7 ( 8) | 8 (10) | 27 ( 8) |
| Coughing | 10 (11) | 2 ( 2) | 25 ( 7) |
| Nocturia | 3 ( 3) | 4 ( 5) | 25 ( 7) |
| Testis disorder | 2 ( 2) | 4 ( 5) | 23 ( 7) |
| Urinary tract infection | 4 ( 4) | 7 ( 8) | 23 ( 7) |
| Pruritus | 8 ( 9) | 2 ( 2) | 21 ( 6) |
| Purpura | 3 ( 3) | 6 ( 7) | 20 ( 6) |
| Sinusitis | 7 ( 8) | 4 ( 5) | 19 ( 5) |
| Hematuria | 5 ( 6) | 3 ( 4) | 18 ( 5) |
| Leg pain | 2 ( 2) | 4 ( 5) | 18 ( 5) |
| Micturition urgency | 1 ( 1) | 0 | 18 ( 5) |
| Anemia | 6 ( 7) | 8 (10) | 17 ( 5) |
| Chest pain | 4 ( 4) | 6 ( 7) | 17 ( 5) |
| Dyspnea | 6 ( 7) | 3 ( 4) | 17 ( 5) |
| Infection | 5 ( 6) | 4 ( 5) | 17 ( 5) |
| Skin disorder | 4 ( 4) | 4 ( 5) | 17 ( 5) |

Events occurring in at least 5% of the abarelix depot group
[1] Includes rash, erythematous rash, or maculopapular rash
Source: Safety Update, Table 6-P, pg 61.

**Medical Officer's Comments**

- **The types and incidences of reported adverse events are compatible with the study population (men with carcinoma of the prostate with a median age of > 70 yrs). For most categories, the reported incidence of adverse events was similar in the abarelix and Lupron groups.**
- **Categories of adverse events in which the percentage of patients reporting an event through Day 169 in the abarelix group exceeded that in the in the Lupron group by ≥ 3%**

**(Table 24) were upper respiratory tract infection, fatigue, and micturition frequency (all 3% higher).**

- **In patients treated for up to 1 year, adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 3% (Table 25) were micturition frequency, headache, accidental injury, nocturia, testis disorder, urinary tract infection, purpura, leg pain, and micturition urgency.**

### 9.5.3 Treatment-Related Adverse Events

All treatment-related adverse events that occurred through Day 169 in the 3 principal safety studies in at least 2% of patients treated with abarelix are pooled across studies and listed in Table 26. Treatment-related adverse events were reported for 136 of 284 (48%) patients in the Lupron group, 48 of 83 (58%) patients in the Lupron plus Casodex group and 373 of 735 (51%) patients in the abarelix group. A similar listing for adverse events that occurred in patients treated for up to 1 year (Studies 149-98-02 and 149-98-03) is presented in Table 27. In patients treated for up to 1 year, adverse events were reported for 37 of 89 (42%) patients in the Lupron group, 51 of 83 (61%) patients in the Lupron plus Casodex group and 181 of 348 (52%) patients in the abarelix group.

**Table 26. Treatment-Related Adverse Events Occurring Through Day 169 in 2% or More of Patients in the Abarelix Group (Studies 149-98-02, 149-98-03, and 149-99-03)**

| Preferred Term | Lupron N = 284 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 735 n (%) |
|---|---|---|---|
| *Any Treatment-Related AE* | *136 ( 48)* | *48 ( 58)* | *373 ( 51)* |
| Fatigue | 34 ( 12) | 12 ( 14) | 106 ( 14) |
| Headache | 19 ( 7) | 7 ( 8) | 61 ( 8) |
| Testis disorder | 12 ( 4) | 2 ( 2) | 35 ( 5) |
| Pain | 10 ( 4) | 2 ( 2) | 30 ( 4) |
| Impotence | 16 ( 6) | 2 ( 2) | 29 ( 4) |
| Micturition frequency | 9 ( 3) | 1 ( 1) | 27 ( 4) |
| Diarrhea | 12 ( 4) | 3 ( 4) | 23 ( 3) |
| Dizziness | 8 ( 3) | 2 ( 2) | 20 ( 3) |
| Libido decreased | 21 ( 7) | 2 ( 2) | 19 ( 3) |
| Rash[1] | 3 ( 1) | 3 ( 4) | 19 ( 3) |
| Weight increase | 2 ( 1) | 0 | 16 ( 2) |
| Flatulence | 5 ( 2) | 3 ( 4) | 15 ( 2) |
| Muscle weakness | 4 ( 1) | 2 ( 2) | 15 ( 2) |
| Pruritus | 5 ( 2) | 1 ( 1) | 15 ( 2) |
| Insomnia | 10 ( 4) | 2 ( 2) | 13 ( 2) |
| Nausea | 11 ( 4) | 1 ( 1) | 13 ( 2) |
| Nocturia | 3 ( 1) | 2 ( 2) | 13 ( 2) |
| Myalgia | 11 ( 4) | 2 ( 2) | 12 ( 2) |

Based on descending order of frequency in the abarelix depot group through Day 169

[1] Rash, erythematous rash, maculopapular rash

Source: Table 6-G, pg 166, ISS Vol 1.108.

**Table 27. Treatment-Related Adverse Events Occurring in 1% or More of Patients in the Abarelix Group With Up to 1 Year of Exposure to Study Drug (Studies 149-98-02 and 149-98-03)**

| | Treatment Group | | |
|---|---|---|---|
| Preferred Term | Lupron N = 89 n (%) | Lupron Plus Casodex N = 83 n (%) | Abarelix N = 348 n (%) |
| *Any Treatment-Related AE* | *37 (42)* | *51 (61)* | *181 (52)* |
| Fatigue | 8 ( 9) | 15 (18) | 50 ( 14) |
| Headache | 6 ( 7) | 7 ( 8) | 31 ( 9) |
| Testis disorder (atrophy) | 1 ( 1) | 3 ( 4) | 20 ( 6) |
| Pain | 3 ( 3) | 4 ( 5) | 18 ( 5) |
| Micturition frequency | 1 ( 1) | 2 ( 2) | 17 ( 5) |
| Dizziness | 2 ( 2) | 2 ( 2) | 12 ( 3) |
| Pruritus | 4 ( 4) | 1 ( 1) | 11 ( 3) |
| Diarrhea | 1 ( 1) | 3 ( 4) | 10 ( 3) |
| Paraesthesia | 0 | 0 | 9 ( 3) |
| Myalgia | 3 ( 3) | 2 ( 2) | 8 ( 2) |
| Nocturia | 0 | 3 ( 4) | 8 ( 2) |
| Rash [1] | 1 ( 1) | 3 ( 4) | 8 ( 2) |
| Testicular pain | 1 ( 1) | 4 ( 5) | 8 ( 2) |
| Anorexia | 1 ( 1) | 1 ( 1) | 7 ( 2) |
| Impotence | 2 ( 2) | 2 ( 2) | 7 ( 2) |
| Muscle weakness | 1 ( 1) | 3 ( 4) | 7 ( 2) |
| Injection site pain | 3 ( 3) | 0 | 6 ( 2) |
| Nausea | 3 ( 3) | 1 ( 1) | 6 ( 2) |
| Somnolence | 1 ( 1) | 1 ( 1) | 6 ( 2) |
| Anemia | 0 | 5 ( 6) | 5 ( 1) |
| Depression | 0 | 3 ( 4) | 5 ( 1) |
| Flatulence | 2 ( 2) | 3 ( 4) | 5 ( 1) |
| Rhinitis | 0 | 3 ( 4) | 5 ( 1) |
| Abdominal pain | 1 ( 1) | 5 ( 6) | 4 ( 1) |
| Alopecia | 2 ( 2) | 0 | 4 ( 1) |
| Constipation | 0 | 6 ( 7) | 4 ( 1) |
| Libido decreased | 2 ( 2) | 2 ( 2) | 4 ( 1) |
| Peripheral edema | 7 ( 8) | 1 ( 1) | 4 ( 1) |
| Arthralgia | 0 | 3 ( 4) | 2 ( 1) |
| Dry Skin | 0 | 2 ( 2) | 2 ( 1) |
| Malaise | 0 | 2 ( 2) | 2 ( 1) |

Events occurring in at least 2% of patients in any treatment group

[1] Includes rash, erythematous rash, or maculopapular rash

Source: Table 6-Q, pg 63, Safety Update.

**Medical Officer's Comments**

- **Adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 2% through Day 169 (Table 26) were fatigue and rash (both by 2%).**
- **In patients treated for up to 1 year, adverse event categories for which the percentage of patients reporting an event in the abarelix group exceeded that in the Lupron group by ≥ 2% (Table 27) were fatigue, headache, testis disorder (atrophy), pain, micturition frequency, diarrhea, paraesthesia, and nocturia.**

- **The percentages of patients experiencing a treatment-related adverse event in the abarelix group were greater than those in the Lupron group (51% vs 48% through Day 169; 52% vs 42% for up to 1 year of treatment). However, the percentages of patients experiencing a treatment-related adverse events in the abarelix group were lower than those in the Lupron plus Casodex group (51% vs 58% through Day 169; 52% vs 61% for up to 1 year of treatment).**
- **The number of adverse categories, for which the percentage of patients was higher in the abarelix group relative to the Lupron group, appeared to increase with increasing duration of treatment (see preceding comments). This apparent relative increase may be misleading and should be accepted with reservation for the following reason. The overall incidence of treatment-related adverse events in patients treated with Lupron for up to 1 year (Study 149-98-02) was reported to be lower than that for the pooled data for patients treated with Lupron for only 6 months in Studies 149-98-02 and 149-99-03, an unlikely occurrence.**

### 9.5.4 Adverse Events Resulting in Patient Withdrawal

The treatment-related adverse events that led to withdrawal of patients from the 3 principal safety studies are summarized and listed by preferred terms in Table 28. Overall, 5 of 284 (1.8%) patients in the Lupron group, 6 of 83 (7.2%) patients in the Lupron plus Casodex group and 19 of 735 (2.6%) patients in the abarelix group were withdrawn because of a treatment related adverse event. (A treatment related adverse event was defined as an adverse event considered to have an unknown, possible, probable, or definite relationship to Study Drug.)

Medical Officer's Comments

- **None of the adverse events resulting in a patient's withdrawal occurred with an incidence of > 2%. The most frequent adverse events (based on percentage of affected patients) were (a) increased hepatic enzymes (2.4%) and fatigue (2.4.%) in the Lupron plus Casodex group, (b) hot flashes (1.1%) in the Lupron group, and (c) increased hepatic enzymes (0.7%) and allergic events (0.8%, includes allergic reactions, urticaria, and rash) in the abarelix group.**
- **Hepatotoxicity is a known complication of treatment with Casodex and other antiandrogens. Hot flashes are an expected consequence of medical castration and are to be expected.**
- **The percentages of patients withdrawn for hepatotoxicity and allergic reactions in the abarelix group, based on this reviewer's assessment of the data, are slightly higher than those represented in Table 28 that are based on the sponsor's assessment. Allergic reactions and hepatotoxicity are reviewed in detail in Sections 9.9.1 and 9.9.2, respectively.**

**Table 28. Withdrawals Due to Treatment-Related Adverse Events (Studies 149-98-02, 149-98-03, 149-99-03)**

| | Lupron | | | Lupron Plus Casodex® | | | Abarelix | | |
|---|---|---|---|---|---|---|---|---|---|
| | Through Day 169 | Beyond Day 169 | Overall | Through Day 169 | Beyond Day 169 | Overall | Through Day 169 | Beyond Day 169 | Overall |
| Evaluable Patients | N = 284 n (%) | N = 79 n (%) | N = 284 n (%) | N = 83 n (%) | N = 71 n (%) | N = 83 n (%) | N = 735 n (%) | N = 325 n (%) | N = 735 n (%) |
| Number of adverse events | 6 | 1 | 7 | 6 | 2 | 8 | 16 | 3 | 19 |
| Withdrawals due to adverse events | 4 ( 1) | 1 (< 1) | 5 ( 2) | 4 ( 5) | 2 ( 3) | 6 ( 7) | 16 ( 2) | 3 ( 1) | 19 ( 3) |
| Preferred Term | | | | | | | | | |
| Hepatic enzymes increased[1] | 0 | 0 | 0 | 2 ( 2) | 0 | 2 ( 2) | 5 ( 1)[2] | 0 | 5 ( 1) |
| Allergic reaction | 0 | 0 | 0 | 0 | 0 | 0 | 4 ( 1)[3] | 0 | 4 ( 1) |
| Depression | 0 | 0 | 0 | 1 ( 1) | 0 | 1 ( 1) | 2 (< 1) | 0 | 2 (< 1) |
| Hot flushes | 2 ( 1) | 1 (< 1) | 3 ( 1) | 1 ( 1) | 0 | 1 ( 1) | 1 (< 1) | 1 (< 1) | 2 (< 1) |
| Anemia | 0 | 0 | 0 | 0 | 0 | 0 | 1 (< 1) | 0 | 1 (< 1) |
| Chest pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (< 1) | 1 (< 1) |
| Fatigue | 1 (< 1) | 0 | 1 (< 1) | 1 ( 1) | 1 ( 1) | 2 ( 2) | 1 (< 1) | 0 | 1 (< 1) |
| Rash | 0 | 0 | 0 | 0 | 0 | 0 | 1 (< 1) | 0 | 1 (< 1) |
| Syncope | 0 | 0 | 0 | 0 | 0 | 0 | 1 (< 1) | 0 | 1 (< 1) |
| Urticaria | 1 (< 1) | 0 | 1 (< 1) | 0 | 0 | 0 | 0 | 1 (< 1) | 1 (< 1) |
| Headache | 1 (< 1) | 0 | 1 (< 1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Insomnia | 1 (< 1) | 0 | 1 (< 1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Libido decreased | 0 | 0 | 0 | 1 ( 1) | 0 | 1 ( 1) | 0 | 0 | 0 |
| Myalgia | 0 | 0 | 0 | 0 | 1 ( 1) | 1 ( 1) | 0 | 0 | 0 |

Based on descending order of frequency in the abarelix depot group (overall)
[1] Includes events of hepatic enzymes increased, SGPT increased, and hepatic function abnormal
[2] One patient with elevated liver enzymes (Patient 50-3085 in Study 149-98-03) elected to withdraw for "personal reasons" and is not included in this listing. Inclusion of this patient would increase the total to 6 patients as in Table 54.
3 The sponsor's assignment of patients to the category of "allergic reaction" as represented in this listing differs somewhat from that used by this reviewer. See Section 9.1.1 for more information about patient withdrawals due to allergic reactions.
Source: Table 6-C, pg 158, ISS Vol 1.108.

### 9.5.5 Severe or Life-Threatening Treatment-Related Adverse Events

Across the 3 controlled studies (Studies 149-98-02, 149-98-03, and 149-99-03), severe or life-threatening adverse events were reported for 60 of 284 patients (21%) in the Lupron group, 21 of 83 patients (25%) in the Lupron plus Casodex group, and 125 of 735 patients (17%) in the abarelix group. Across these same studies, treatment-related, severe or life-threatening adverse events were reported for 15 of 284 patients (5%) in the Lupron group, 2 of 83 patients (2%) in the Lupron plus Casodex group, and 23 of 735 patients (3%) in the abarelix group. The treatment-related, severe or life-threatening adverse events experienced by patients treated with abarelix are listed by patient in Table 29.

**Medical Officer's Comment**

- **Many of these severe or life threatening adverse events are not unexpected in a population of elderly men with prostate cancer. Others would be expected as a consequence of decreased testosterone levels resulting from treatment with abarelix.**
- **Three of the patients experienced severe increases in transaminases and 5 of the patients (includes patients 16-3028 and 333-3336) experienced allergic reactions. Allergic reactions and hepatotoxicity are reviewed in Sections 9.9.1 and 9.9.2, respectively.**

**Table 29. Severe or Life-Threatening Treatment-Related Adverse Events in Abarelix Treatment Groups (Pooled Studies 149-98-02, 149-98-03, and 149-99-03)**

| Study No. | Patient No. | Age (yr) | Race[1] | Preferred Term | Verbatim Description | Onset Day | Event Duration (days) | Relationship |
|---|---|---|---|---|---|---|---|---|
| 149-98-02 | 37-2085 | 63 | C | Libido decreased | Decreased Libido | 24 | NR [2] | Definite |
| | 13-2149 | 75 | C | Aggravated depression | Worsening depression | 110 | 19 | Possible |
| | | | | Neurosis | Suicidal ideations | 114 | 15 | Possible |
| | 37-2160 | 50 | H | Hepatic enzymes increased | Elevated transaminases | 29 | 164 | Definite |
| | 13-2178 | 54 | C | Headache | Headache | 21 | 3 | Possible |
| | 11-2218 | 71 | C | Allergic reaction | Drug reaction | 15 | 1 | Definite |
| 149-98-03 | 50-3018 | 75 | C | Hepatic enzymes increased | Elevated liver enzymes | 169 | 13 | Possible |
| | 16-3028 | 75 | A | Flushing | Whole body warmth | 169 | 1 | Probable |
| | | | | Erythematous rash | Whole body redness | 169 | 1 | Probable |
| | 50-3085 | 62 | C | Elevated AST | Elevated AST | 253 | NR | Possible |
| | 71-3108 | 71 | AA | Depression | Depression | 107 | NR | Possible |
| | 50-3175 | 79 | C | Pain | Pain lower arms and bottom rib cage | 15 | 1 | Unknown |
| | 09-3246 | 81 | C | Allergic reaction | Allergic reaction | 85 | 1 | Definite |
| 149-99-03 | 310-1032 | 58 | AA | Micturition frequency | Exacerbation of urinary frequency | 74 | NR | Unknown |
| | | | | Micturition urgency | Exacerbation of urinary urgency | 74 | NR | Unknown |
| | 390-1206 | 71 | C | Urinary tract infection | Urinary tract irritation | 28 | 17 | Possible |
| | 350-1357 | 63 | C | Impotence | Impotence | 54 | NR | Definite |
| | 314-1385 | 78 | C | Hot flushes | Intolerable hot flashes | 140 | NR | Definitely |
| | 357-1448 | 83 | C | Pain | Pain right shoulder | 13 | NR | Unknown |
| | 306-1544 | 87 | C | Fatigue | Fatigue | 30 | 51 | Possible |

[1] Race: C = Caucasian, AA = African American, H= Hispanic, A = Asian.
[2] NR = Not Resolved.

(Continued)

**Table 29. Severe or Life-Threatening Treatment-Related Adverse Events in Abarelix Treatment Groups (Pooled Studies 149-98-02, 149-98-03, and 149-99-03) (Continued)**

| Study No. | Patient No. | Age (yr) | Race[1] | Preferred Term | Verbatim Description | Onset Day | Event Duration (days) | Relationship |
|---|---|---|---|---|---|---|---|---|
| 149-99-03 | 337-2016 | 57 | AA | Headache | Worsening headaches | 18 | 52 | Possible |
| (Continued) | 377-2060 | 63 | C | Back pain | Flank pain | 125 | 18 | Unknown |
| | 391-2358 | 70 | C | Fatigue | Fatigue | 40 | NR | Probable |
| | | | | Somnolence | Lethargy | 40 | NR | Probable |
| | 391-2522 | 63 | C | Depression | Depression | 12 | 158 | Probable |
| | 313-3087 | 74 | A | Allergic reaction | Systemic allergic response | 56 | 1 | Probable |
| | 333-3336 | 72 | C | Syncope | Vasovagal reaction | 15 | 1 | Unknown |

[1] Race: C = Caucasian, AA = African American, H= Hispanic, A = Asian.
[2] NR = Not Resolved
Source: Table 6-H, ISS and Table 6-S, pg 66, Safety Update.

### 9.5.6 Nonfatal, Serious Treatment-Related Adverse Events

Across the 3 controlled studies (Studies 149-98-02, 149-98-03, and 149-99-03), nonfatal serious adverse events were reported for 35 of 284 patients (12%) in the Lupron group, 15 of 83 patients (18%) in the Lupron plus Casodex group, and 89 of 735 patients (12%) in the abarelix group. Across these same studies, treatment-related nonfatal serious adverse events were reported for 3 of 284 patients (1%) in the Lupron group, 2 of 83 patients (2%) in the Lupron plus Casodex group, and 12 of 735 patients (2%) in the abarelix group. The treatment-related nonfatal serious adverse events in the controlled studies are listed by treatment group and patient in Table 30.

**Medical Officer's Comments**

- **Of the 12 nonfatal serious adverse events in the abarelix-treated patients, 6 were cutaneous or systemic allergic reactions and 4 were related to hepatic toxicity. Allergic reactions and hepatotoxicity in abarelix-treated patients are reviewed in Sections 9.9.1 and 9.9.2, respectively.**
- **Two patients in the Lupron plus Casodex group experienced serious adverse events related to elevations in transaminases. Increased transaminases are an expected adverse effect in patients treated with antiandrogens such as Casodex.**

## 9.6 Deaths

In the 3 principal, controlled safety studies, a total of 12 patients died (1 in the Lupron group and 11 in the abarelix group), either during the treatment period (within 28 days of the last dose of Study Drug) or during the posttreatment follow up period (Table 31). In the uncontrolled studies (Studies 149-97-04, 149-98-04, and 149-99-04), 16 patients treated with abarelix died, either during the treatment period or during the posttreatment follow up period (Table 32). Ten (10) of the 27 deaths in abarelix-treated patients were attributed to progression of their prostate cancer.

**Medical Officer's Comments**

- **Of the 27 deaths in abarelix-treated patients, 10 were directly attributed to progression of prostate cancer. End-of-treatment testosterone data were available for 9 of these patients. All were suppressed to ≤ 50 ng/dL at the time of their last assessment.**
- **Of the remaining 17 deaths, 8 were a result of a cardiovascular adverse event (myocardial infarction, stroke, or pulmonary embolus), 5 were attributed to respiratory/infectious causes (pneumonia, empyema, or chronic obstructive lung disease), 3 were attributed to coexisting carcinomas (pulmonary or pancreatic), and 1 was due to aspiration.**
- **Nineteen (19) of the 27 deaths occurred within 35 days of the patient's last dose of abarelix. Six (6) deaths occurred within 36-70 days of the last dose of abarelix.**
- **Although the proportion of abarelix-treated patients in the controlled studies who died (11 of 735, 1.4%) was greater than that of the active control-treated patients (1 of 367, 0.3%), it is likely, as reported by the Investigators, that none of these deaths was a result of treatment with abarelix.**

**Table 30. Nonfatal, Serious Treatment-Related Adverse Events (Pooled Studies 149-98-02, 149-98-03, 149-99-03)**

| Study | Patient No. | Preferred Term (verbatim description) | Onset (day) | Severity | Relationship to Treatment |
|---|---|---|---|---|---|
| Lupron Treatment Group (N = 284) | | | | | |
| 149-98-02 | 46-2065 | Fall (collapse without syncope) | 286 | Moderate | Possible |
| 149-99-03 | 301-1295 | Urticaria acute (acute urticaria) | 67 | Severe | Definite |
| | 328-3084 | Ketosis (diabetic ketoacidosis) | 80 | Severe | Probable |
| Lupron Casodex Treatment Group (N = 83) | | | | | |
| 149-98-03 | 27-3049 | Hepatic enzymes increased (elevated transaminases) | 43 | Moderate | Definite |
| | 01-3144 | SGPT increased (elevated SGPT) | 57 | Moderate | Possible |
| Abarelix Depot Treatment Group ( N = 735) | | | | | |
| 149-98-02 | 37-2160 | Hepatic enzymes increased (elevated transaminases) | 29 | Severe | Definite |
| | 11-2218 | Allergic reaction (drug reaction) | 15 | Severe | Definite |
| 149-98-03 | 09-3036 | Hepatic enzymes increased (elevated liver function tests) | 29 | Moderate | Definite |
| | 50-3085 | Hepatitis (chemical hepatitis) | 253 | Moderate | Probable |
| | 27-3200 | Urticaria (urticaria) | 197 | Mild | Definite |
| | 76-3224 | Allergic reaction (allergic reaction) | 29 | Mild | Probable |
| | 09-3246 | Allergic reaction (allergic reaction) | 85 | Severe | Definite |
| 149-99-03 | 313-1063 | Migraine aggravated (exacerbation of migraine HA) | 21 | Moderate | Possible |
| | 338-1259 | Hepatic enzymes increased (elevated transaminases) | 29 | Moderate | Possible |
| | 357-2226 | Rash (rash) | 85 | Moderate | Definite |
| | 313-3087 | Allergic reaction (systemic allergic response) | 56 | Life-threatening | Probable |
| | 333-3336 | Syncope (vasovagal reaction) | 15 | Severe | Unknown |

Source: Safety Update - Table 6-D and Table 6-O

**Table 31. Listing of Patients Who Died During or Following Treatment with Abarelix or Lupron (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)**

| Study | Patient Number | Age (yr) | Race[1] | Cause of Death | Last Dose (day) | Day of Death | Days From Last Dose |
|---|---|---|---|---|---|---|---|
| *Lupron (N = 284)* | | | | | | | |
| 149-98-02 | 22-2119 | 80 | C | Myocardial infarction | 308 | 338 | 30 |
| *Lupron Plus Casodex (N= 83)* | | | | | | | |
| | | | | No Deaths | | | |
| *Abarelix Depot (N = 735)* | | | | | | | |
| 149-98-02 | 22-2031 | 73 | C | Pulmonary carcinoma | 309 | 349 | 40 |
| 149-98-02 | 41-2075 | 72 | C | Cardiac failure | 253 | 305 | 52 |
| 149-98-02 | 41-2120 | 85 | C | Pulmonary carcinoma | 253 | 290 | 37 |
| 149-98-02 | 41-2137 | 77 | C | Intracranial hemorrhage | 197 | 214 | 17 |
| 149-98-02 | 42-2254 | 68 | C | Myocardial infarction | 179 | 187 | 8 |
| 149-98-03 | 71-3189 | 51 | C | Metastatic prostate cancer | 86 | 123 | 37 |
| 149-99-03 | 317-1216 | 67 | C | Pancreatic carcinoma | 29 | 115 | 86 |
| 149-99-03 | 392-1399 | 79 | C | Chr obstruct. lung disease | 113 | 185 | 72 |
| 149-99-03 | 341-1540 | 89 | C | Empyema right lung | 85 | 101 | 16 |
| 149-99-03 | 308-2093 | 80 | C | Pneumonia | 113 | 134 | 21 |
| 149-99-03 | 330-3443 | 61 | AA | Metastatic prostate cancer | 149 | 165 | 16 |

[1] Race: C = Caucasian, AA = African American
Source: Data Listing 2.1 (ISS, Vol. 1.110)

**Table 32. Listing of Patients Who Died During or Following Treatment with Abarelix (Uncontrolled Studies 149-97-04, 149-98-04, and 149-99-04)**

| Patient Number | Age | Race | Cause of death | Last Dose (Day) | Day of Death | Days From Last Dose |
|---|---|---|---|---|---|---|
| *Study 149-97-04* | | | | | | |
| 37-4766 | 54 | C | Acute myocardial infarction | 309 | 321 | 12 |
| 38-4775 | 63 | C | Metastatic prostate carcinoma | 454 | 466 | 12 |
| 02-4760 | 82 | C | Bronchial aspiration | 252 | 291 | 39 |
| 22-4763 | 81 | C | Metastatic prostate carcinoma | 85 | 154 | 69 |
| *Study 149-98-04* | | | | | | |
| 402-4030 | 71 | C | Progression of prostate cancer | 85 | 118 | 33 |
| 477-4043 | 79 | C | Progression of prostate cancer | 168 | 188 | 20 |
| 409-4044 | 94 | C | Progression of prostate cancer | 29 | 45 | 16 |
| 441-4050 | 89 | C | Pulmonary embolus | 29 | 61 | 32 |
| 477-4064 | 77 | C | Renal failure 2nd to prostate cancer | 142 | 149 | 7 |
| 499-4101 | 55 | H | Progression of prostate cancer | 197 | 216 | 19 |
| *Study 149-99-04* [4] | | | | | | |
| 12-3027 | 84 | C | Massive stroke | 400 [2] | 422 [3] | 22 |
| 38-3179 | 72 | C | Pneumonia | 393 | 406 | 13 |
| 441-4036 | 94 | C | Metastatic prostate cancer | 253 | 274 | 21 |
| 442-4037 | 69 | C | Myocardial infarction | 174 | 200 | 26 |
| 428-4005 | 77 | C | Pneumonia | 310 | 339 | 29 |
| 383-1366 | 82 | C | Subendocardial infarction | 282 | 301 | 19 |

[1] Race: C = Caucasian, H = Hispanic
[2] For all patients in Study 149-99-04, number represents cumulative dosing from prior study and study 149-99-04.
[3] For all patients in Study 149-99-04, number represents cumulative study days from prior study and study 149-99-04.
[4] Patients previously enrolled in controlled Studies 149-98-02, 149-98-03, or 149-00-03.
Source: Table 10-7, Vol. 91 (Study 97-04); Table 10-9, Vol. 1 (Final Report for Study 149-98-04); Table 8-K, Safety Update (Study 149-99-04).

## 9.7 Laboratory Assessments

**Medical Officer's Comments**

Laboratory data for the 3 principal safety studies were reviewed by the following process:

- Mean values, median values, and mean changes from baseline values for each laboratory test at protocol-designated assessment times were reviewed for differences across treatment groups.
- Percentages of patients with laboratory values that shifted to outside of the normal range on one more or more occasions during treatment were reviewed for differences across treatment groups. Shift tables containing selected test values are provided in this review.
- Notable laboratory values (abnormal values that were considered to be of particular concern based on the Sponsor's criteria) were reviewed.

### 9.7.1 Hematology Assessments

#### 9.7.1.1 Mean Changes From Baseline Values

**Medical Officer's Comment**

- **There were no remarkable or consistent differences in mean changes from baseline values in the pooled hematology values from the 3 principal safety studies. Isolated or intermittent changes for some measurements at some assessment times were noted but**

**no consistent patterns suggestive of increased toxicity in the abarelix groups were observed.**

### 9.7.1.2 Shifts to Outside of the Normal Range

Percentages of patients with selected hematology values that shifted to outside of the normal range on one more or more occasions during treatment are presented Table 33. For each measurement, the percentage of patients with a shift to low (i.e., normal to low, high to low, and unknown to low) or a shift to high (i.e., normal to high, low to high, and unknown to high) is listed. Data are also presented separately for changes that were observed between Study Days 1-169 (pooled data from Studies 149-98-02, 149-98-03, and 149-99-03) and between Study Days 1-365 (pooled data from only Studies 149-98-02 and 149-98-03).

Medical Officer's Comments

- **For the pooled data for the period from Day 1-169, all differences between the abarelix group and the Lupron group or the Lupron plus Casodex group were ≤ 3% with the following exceptions. Differences of >3% in shifts from normal to low included: a greater percentage of Lupron or Lupron plus Casodex patients shifting to low for the categories of hematocrit, WBC, and neutrophils. The percentages of patients who shifted from normal to high for eosinophils was higher in the Lupron group (14%) and the Lupron plus Casodex group (17%) than in the abarelix group (10%).**
- **For the period from Day 1-365, in which data from only Studies 149-98-02 and 149-98-03 were assessed, there were no remarkable differences between the abarelix and Lupron groups. Differences of >4% in shifts from normal to low or high included: (a) a greater percentage of Lupron patients shifting to low for the categories of hemoglobin and hematocrit, (b) a greater percentage of abarelix patients shifting to low for the category of white blood cells, and (3) a greater percentage of Lupron patients shifting to high for the category of eosinophils (23% vs 15%). It is not known it these differences between the Day 1-169 and Day 1-365 comparisons are a result of chance and the smaller sample size in the Day 1-365 comparison (more likely in this reviewer's opinion) or the longer treatment period.**

### 9.7.1.3 Clinically Notable Hematology Values

The sponsor defined upper and lower limits for selected hematology values (clinically notable hematology values) that represented changes of particular clinical significance. Table 34 summarizes the number and percentage of subjects in the 3 principal safety studies that exhibited clinically notable hematology values. Overall the number of such patients was low, although the highest percentages of such changes in virtually each category was observed in the pooled abarelix group.

Medical Officer's Comment

- **The greatest differences between the abarelix and the Lupron groups were observed for decreases in hemoglobin and increases in WBC values. Twenty of 735 (2.7%) patients in the abarelix group, compared to 4 of 284 (1.4%) patients in the Lupron group, had hemoglobin values below 9.5 g/dL. Of these 24 subjects, only one, a patient in the abarelix group, had a hemoglobin value below 8.0 g/dL. In the abarelix group, a 2-fold higher percentage of patients (1.8% of the abarelix group vs 0.7% of the Lupron group) had WBC values of greater than 15,000/μL.**
- **Considering the study populations, namely elderly men with prostate cancer and other serious medical problems, the absolute number of clinically notable hematology values and the differences across groups are not particularly worrisome.**

**Table 33. Hematology Value Shifts to Outside the Normal Range (Studies 149-98-02, 149-98-03, 149-99-03)**

| | Lupron (N=284) | | | | Lupron +Casodex (N=83) | | | | Abarelix (N=735) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Shift to Low[1] | | Shift to High[2] | | Shift to Low | | Shift to High | | Shift to Low | | Shift to High | |
| | Eval[3] | Shift | Eval[3] | Shift | Eval | Shift | Eval | Shift | Eval | Shift | Eval | Shift |
| Test | N | (%) | N | (%) | N | (%) | n | (%) | N | (%) | n | (%) |
| Hemoglobin | | | | | | | | | | | | |
| Days 1-169[4] | 264 | (27) | 279 | ( 1) | 77 | (23) | 79 | ( 1) | 690 | (25) | 716 | ( 1) |
| Days 1-365[5] | 80 | (48) | 89 | ( 1) | 77 | (31) | 79 | ( 1) | 335 | (36) | 338 | ( 1) |
| Hematocrit | | | | | | | | | | | | |
| Days 1-169 | 271 | (32) | 280 | ( 1) | 80 | (28) | 80 | ( 0) | 687 | (28) | 721 | ( 1) |
| Days 1-365 | 85 | (47) | 89 | ( 2) | 08 | (49) | 80 | ( 0) | 334 | (42) | 342 | ( 1) |
| White Blood Cell | | | | | | | | | | | | |
| Days 1-169 | 273 | ( 8) | 277 | ( 4) | 79 | (14) | 77 | ( 5) | 693 | (10) | 710 | ( 5) |
| Days 1-365 | 87 | (11) | 88 | ( 5) | 79 | (15) | 77 | ( 6) | 328 | (18) | 343 | ( 6) |
| Platelet | | | | | | | | | | | | |
| Days 1-169 | 276 | ( 1) | 279 | ( 4) | 79 | ( 3) | 81 | ( 5) | 713 | ( 3) | 724 | ( 6) |
| Days 1-365 | 87 | ( 2) | 88 | ( 6) | 79 | ( 5) | 81 | ( 7) | 342 | ( 4) | 346 | ( 9) |
| Neutrophils | | | | | | | | | | | | |
| Days 1-169 | 283 | ( 5) | 264 | (17) | 78 | ( 6) | 78 | (14) | 723 | ( 2) | 678 | (17) |
| Days 1-365 | 89 | ( 6) | 82 | (26) | 78 | ( 8) | 78 | (22) | 344 | ( 4) | 325 | (23) |
| Lymphocytes | | | | | | | | | | | | |
| Days 1-169 | 264 | (17) | 280 | ( 5) | 78 | (15) | 78 | ( 4) | 682 | (16) | 722 | ( 2) |
| Days 1-365 | 82 | (27) | 88 | ( 5) | 78 | (19) | 78 | ( 5) | 328 | (23) | 344 | ( 5) |
| Eosinophils | | | | | | | | | | | | |
| Days 1-169 | 283 | ( 0) | 277 | (14) | 81 | ( 0) | 77 | (17) | 729 | ( 0) | 706 | (10) |
| Days 1-365 | 89 | ( 0) | 87 | (23) | 81 | ( 0) | 77 | (17) | 348 | ( 0) | 337 | (15) |

[1] Shifts to low include normal to low, high to low, and unknown to low.
[2] Shifts to high include normal to high, low to high, and unknown to high.
[3] Patients whose baseline value was not low (shift to low) or not high (shift to high) and who had a least 1 lab result in the specified period.
[4] Includes Studies 149-98-02, 149-98-03, and 149-99-03.
[5] Includes only Studies 149-98-02 and 149-98-03.
Source: Modified from Tables 5.1.2 & 5.2.2 from ISS and Table 4.1.1 of Safety Update.

**Table 34. Clinically Notable Hematology Values (Studies 149-98-02, 149-98-03, 149-99-03)**

| | Treatment Group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Lupron (N=284) | | | Lupron + Casodex (N=83) | | | Abarelix (N=735) | | |
| | Eval n | Experienced[1] n | (%) | Eval n | Experienced n | (%) | Eval n | Experienced n | (%) |
| Hemoglobin | | | | | | | | | |
| <8.0 g/dL | 283 | 0 | | 82 | 0 | | 734 | 1 | (0.1) |
| <9.5 g/dL | 283 | 4 | (1.4) | 82 | 2 | (2.4) | 733 | 19 | (2.6) |
| >19.0 g/dL | 283 | 0 | | 82 | 0 | | 733 | 0 | |
| Hematocrit | | | | | | | | | |
| <24% | 283 | 0 | | 82 | 0 | | 733 | 1 | (0.1) |
| >55% | 283 | 0 | | 82 | 0 | | 733 | 1 | (0.1) |
| Platelet count | | | | | | | | | |
| <75,000/μL | 282 | 2 | (0.7) | 83 | 0 | | 733 | 4 | (0.5) |
| White blood cell count | | | | | | | | | |
| <2,000/μL | 282 | 0 | | 83 | 0 | | 733 | 1 | (0.1) |
| >15,000/μL | 282 | 2 | (0.7) | 83 | 0 | | 733 | 13 | (1.8) |

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

### 9.7.2 Chemistry Assessments

Laboratory data for tests of liver function (e.g., bilirubin) or of liver injury (e.g., transaminases) are presented and reviewed separately in Section 9.9.2.

#### 9.7.2.1 Mean Changes from Baseline Values

**Medical Officer's Comment**

- **There were no remarkable or consistent differences (with one exception) in mean changes from baseline values in the pooled chemistry values from the 3 principal safety studies. Isolated or intermittent changes for some measurements at some assessment times were noted but no consistent patterns suggestive of increased toxicity in the abarelix groups were observed.**
- **The exception was serum triglyceride levels that tended to be higher in the abarelix group (see Table 35). Mean fasting serum triglyceride levels were numerically higher by 10-15 mg/dL in the abarelix group compared to the Lupron group in the controlled safety studies. This difference was more apparent when the absolute changes from baseline within each treatment group were reviewed, with the increases from baseline for fasting triglycerides ranging from 10.5 to 21.9 mg/dL in the abarelix group. The differences across treatment groups were even greater when the abarelix group was compared to the Lupron plus Casodex group.**
- **These increases in mean fasting serum triglyceride levels, although not desirable, are not a significant safety concern in the population likely to be treated with abarelix.**

**Table 35. Mean Fasting Serum Triglycerides (mg/dL) and Mean Changes from Baseline during Treatment (Controlled Studies 149-98-02, 149-98-03, and 149-99-03)**

| Statistic | Mean Fasting Triglycerides (mg/dL) | | |
|---|---|---|---|
| | Lupron (N = 284) | Lupron +Casodex (N= 83) | Abarelix (N = 735) |
| Baseline | | | |
| Mean | 177 | 190 | 178 |
| Day 85 | | | |
| Mean | 188 | 190 | 201 |
| Mean change | 9.1 | -2.9 | 21.9 |
| N | (272) | (80) | (704) |
| Day 169 | | | |
| Mean | 190 | 180 | 200 |
| Mean change | 13.1 | -17.6 | 19.7 |
| N | (251) | (69) | (660) |
| Day 253 | | | |
| Mean | 183 | 171 | 199 |
| Mean change | -6.0 | -28.2 | 10.5 |
| N | (52) | (40) | (209) |
| Day 337 | | | |
| Mean | 185 | 185 | 200 |
| Mean change | -9.0 | -20.6 | 11.5 |
| N | (51) | (35) | (185) |

Source: March 27, 2001 Supplemental Chemistry Analyses, Table: 5.6.1.1.

### 9.7.2.2 Shifts to Outside of the Normal Range

Percentages of patients with selected chemistry values that shifted to outside of the normal range on one more or more occasions during treatment are presented in Table 36. Data are presented separately for changes that were observed between Study Days 1-169 (pooled data from Studies 149-98-02, 149-98-03, and 149-99-03) and between Study Days 1-365 (pooled data from only Studies 149-98-02 and 149-98-03).

**Medical Officer's Comments**

- **Differences of ≥ 5 in the percentage of patients who shifted to high in the abarelix group compared to the Lupron group were observed for potassium (both treatment periods), BUN (Days 1-169 only), and triglycerides (both treatment periods). The difference in the percentage of patient that shifted to high for triglycerides was even greater when the abarelix group was compared to the Lupron plus Casodex group. A difference of ≥ 5 in the percentage of patients who shifted to high in the Lupron group compared to the abarelix group was observed only for creatinine (Days 1-365).**
- **Differences of ≥ 5 in the percentage of patients who shifted to low in the abarelix group compared to the Lupron group were observed for total protein (Days 1-365 only) and HDL cholesterol (Days 1-365 only). However, a numerically greater percentage of patients in the Lupron plus Casodex group shifted to low for HDL cholesterol than in the abarelix group. The reported high percentage of patients in all treatment groups that shifted to low for total cholesterol is surprising and of unknown significance.**
- **The higher percentage of abarelix-treated patients who showed shifts to high in their serum triglyceride levels is in agreement with the observations reported in Section 9.7.2.1.**

**Of note, there was no significant differences between the Lupron and abarelix groups in terms of the percentage of patients who had a shift to high for total cholesterol.**

- **The pattern of increases in serum triglyceride levels in shown in greater detail in Table 37 in which the magnitude of the increases, based on WHO Toxicity Grades, is represented. The largest relative increase was observed in Toxicity Grade 1.**
-

### 9.7.2.3 Clinically Notable Chemistry Values

The sponsor defined upper and lower limits for selected chemistry values (clinically notable hematology values) that represented changes of particular clinical significance. Table 38 summarizes the number and percentage of subjects in the 3 principal safety studies that exhibited clinically notable chemistry values. For most laboratory assessments, the number of such patients exhibiting notable chemistry values was low.

Medical Officer's Comments

- **In general, the percentages of patients exhibiting notable chemistry values was similar across the treatment groups. Categories showing the highest percentages of these notable values included BUN and creatinine as would be expected in elderly men with prostate cancer.**

**Table 36. Chemistry Value Shifts to Outside the Normal Range (Studies 149-98-02, 149-98-03, 149-99-03) [A]**

| | Lupron (N=284) | | | | Lupron +Casodex (N=83) | | | | Abarelix (N=735) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Shift to Low[1] | | Shift to High[2] | | Shift to Low | | Shift to High | | Shift to Low | | Shift to High | |
| | Eval[3] | Shift | Eval[3] | Shift | Eval | Shift | Eval | Shift | Eval | Shift | Eval | Shift |
| Test | N | (%) | n | (%) | N | (%) | n | (%) | N | (%) | n | (%) |
| Potassium | | | | | | | | | | | | |
| Days 1-169 [4] | 280 | ( 1) | 278 | ( 2) | 81 | ( 2) | 76 | ( 5) | 727 | ( 2) | 716 | ( 7) |
| Days 1-365 [5] | 86 | ( 1) | 87 | ( 3) | 81 | ( 4) | 76 | ( 7) | 347 | ( 3) | 341 | ( 9) |
| BUN | | | | | | | | | | | | |
| Days 1-169 | 283 | ( 0) | 251 | (24) | 81 | ( 0) | 67 | (16) | 730 | ( 0) | 649 | (30) |
| Days 1-365 | 89 | ( 0) | 81 | (33) | 81 | ( 0) | 67 | (21) | 348 | ( 0) | 314 | (36) |
| Creatinine | | | | | | | | | | | | |
| Days 1-169 | 283 | ( 0) | 250 | (11) | 81 | ( 0) | 67 | ( 7) | 730 | (<1) | 657 | (12) |
| Days 1-365 | 89 | ( 0) | 81 | (23) | 81 | ( 0) | 67 | (15) | 348 | ( 1) | 309 | (16) |
| Total Protein | | | | | | | | | | | | |
| Days 1-169 | 281 | ( 2) | 271 | ( 8) | 81 | ( 1) | 80 | (13) | 729 | ( 3) | 705 | ( 7) |
| Days 1-365 | 88 | ( 1) | 84 | ( 7) | 81 | ( 2) | 80 | (14) | 347 | ( 6) | 345 | ( 8) |
| Cholesterol | | | | | | | | | | | | |
| Days 1-169 | 204 | (23) | 279 | ( 4) | 55 | (20) | 81 | ( 2) | 530 | (19) | 718 | ( 5) |
| Days 1-365 | 57 | (37) | 88 | ( 3) | 55 | (25) | 81 | ( 4) | 236 | (32) | 344 | ( 5) |
| Triglycerides | | | | | | | | | | | | |
| Days 1-169 | 279 | ( 3) | 239 | (29) | 81 | ( 6) | 64 | (14) | 722 | ( 2) | 625 | (38) |
| Days 1-365 | 87 | ( 2) | 75 | (31) | 81 | (11) | 64 | (20) | 345 | ( 3) | 283 | (45) |
| HDL | | | | | | | | | | | | |
| Days 1-169 | 252 | ( 4) | 274 | ( 5) | 73 | (11) | 81 | ( 7) | 648 | ( 6) | 721 | ( 6) |
| Days 1-365 | 79 | ( 3) | 88 | ( 7) | 73 | (15) | 81 | ( 9) | 308 | ( 11) | 344 | ( 7) |

[A] Liver function test are presented separately in Tables 45 to 50.
[1] Shifts to low include normal to low, high to low, and unknown to low.
[2] Shifts to high include normal to high, low to high, and unknown to high.
[3] Patients whose baseline value was not low (shift to low) or not high (shift to high) and who had a least 1 lab result in the specified period.
[4] Includes Studies 149-98-02, 149-98-03, and 149-99-03.
[5] Includes only Studies 149-98-02 and 149-98-03.
Source: Modified from Table 5.4.2.1, supplemental safety submission, March 27, 2001.

**Table 37. Triglyceride Shifts in Toxicity Grade - Baseline to Most Extreme On-Study Value on Study Days 85 and 169 (Pooled Data from Controlled Studies 149-98-02, 149-98-03, and 149-99-03)**

| | | Baseline | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Lupron Depot [n, (%)] | | | | | | Lupron Depot + Casodex [n, (%)] | | | | | | Abarelix Depot [n, (%)] | | | | | |
| | Grade | 0 | 1 | 2 | 3 | 4 | Total | 0 | 1 | 2 | 3 | 4 | Total | 0 | 1 | 2 | 3 | 4 | Total |
| Highest On Study Grade | N/A | 10 | 1 | 0 | 0 | 0 | 11 | 3 | 0 | 0 | 0 | 0 | 3 | 1 | 0 | 0 | 0 | 0 | 25 |
| | 0 | 197 (72) | 12 (4) | 1 (<1) | 0 | 0 | 210 | 58 (73) | 4 (5) | 1 (1) | 0 | 0 | 63 | 475 (67) | 18 (3) | 2 (<1) | 1 (<1) | 0 | 496 |
| | 1 | 25 (9) | 15 (5) | 1 (<1) | 0 | 0 | 41 | 4 (5) | 4 (5) | 1 (1) | 0 | 0 | 9 | 106 (15) | 39 (5) | 7 (1) | 1 (<1) | 0 | 153 |
| | 2 | 5 (2) | 5 (2) | 4 (1) | 1 (<1) | 0 | 15 | 1 (1) | 2 (3) | 1 (1) | 0 | 0 | 4 | 21 (3) | 14 (2) | 5 (1) | 0 | 0 | 40 |
| | 3 | 2 (1) | 0 | 0 | 0 | 0 | 2 | 0 | 1 (1) | 2 (3) | 0 | 0 | 3 | 3 (<1) | 8 (1) | 4 (1) | 0 | 2 (<2) | 17 |
| | 4 | 1 (<1) | 1 (<1 | 1 (<1 | 0 | 2 (1) | 5 | 0 | 1 (1) | 0 | 0 | 0 | 1 | 1 (<1) | 0 | 1 (<1) | 2 (<2) | 0 | 4 |
| | Total | 240 | 34 | 7 | 1 | 2 | 284 | 66 | 12 | 5 | 0 | 0 | 83 | 630 | 80 | 19 | 4 | 2 | 735 |

[1] Toxicity Grade: 0 = ≤1.25 x ULN; 1 = 1.26 -< 2.6 x ULN; 2 = 2.6 - < 5.1 x ULN; 3 = 5.1 – 10 x ULN; 4 = > 10 x ULN
Source: Table 5.6.3, pg 188, Vol 1.110