## Tab 6 Safety Review

### 6.1 General Adverse Event Profile

6.1.1 How many subjects were exposed to Combidex during the clinical trials and what was the distribution by dose and method of administration, and by demographics?

In the original NDA submission, 947 subjects received at least one dose of Combidex. In this NDA resubmission, the safety experience was enhanced by the addition of 1,114 subjects. Therefore this safety review covers a total of 2,061 subjects who had received at least one dose of Combidex ranging from 0.3 -3.4 mg Fe/kg as of May 31, 2004. The method of administration used in the clinical trials includes direct bolus injection, 50 mL dilution/slow infusion and 100mL dilution/slow infusion. Table 6.1.1.1 shows the number of subjects by dose and method of administration, and Table 6.1.1.2 shows demographics by method of administration.

**Table 6.1.1.1 Number and percentage of subjects who received Combidex by dose and the method of administration (Combidex clinical program as of May 31, 2004)**

| Dose (mg Fe/kg) | Method of Administration | | | Total |
|---|---|---|---|---|
| | Direct | 50 mL dilution | 100 mL dilution | |
| 0.3 – 1.7 | 129 | 38 | 324 | 491 |
| 2.6 | 2 | 326 | 1,236 | 1,564 |
| 3.4 | -- | -- | 6 | 7 |
| Total | 131 | 364 | 1,566 | 2,061 |

**Table 6.1.1.2 Demographic distribution by method of administration**

| Demographics | Method of Administration | | | Total |
|---|---|---|---|---|
| | Direct bolus injection (n=131) | 50 mL dilution slow infusion (n=364) | 100 mL dilution slow infusion (n=1,556) | (n=2,061) |
| Age > 65 | 27% | 32% | 32% | 32% |
| Female | 46% | 37% | 39% | 39% |
| Weight > 70 kg | 63% | 74% | 56% | 59% |
| History of Allergy Reaction | 3% | 8% | 10% | 9% |

***Comments:*** *Approximately 60% (1236/2061) of subjects received the proposed clinical dose and method of administration (2.6 mg Fe/kg diluted in 100 mL saline/slow infusion over 30 minutes). Thirty-two (32%) of those 2,061 subjects were 65 years and older and 39% were female. The percent of subjects who had a previous history of allergic reaction appeared to be lower in direct bolus injection group (3%), compared to that in other two groups (8-10%).*

6.1.2 What was adverse event profile by the method of administration?

Table 6.1.2.1 shows the adverse events that occurred in more than 0.5% of subjects by method of administration. The five most frequent adverse events were vasodilation, back pain, rash, urticaria and pruritus. These events occurred in approximately in 2-4% of subjects. Most of those events were mild to moderate and occurred within 3 hours of dose administration.

**Table 6.1.2.1 Adverse events (with frequency of occurrence ≥ 0.5%) by method of administration**

| Adverse Events | Method of Administration | | | Total |
|---|---|---|---|---|
| | Direct bolus injection (n=131) | 50 mL dilution slow infusion (n=364) | 100 mL dilution slow infusion (n=1,556) | (n=2,061) |
| Vasodilation | 11.4% | 3.6% | 3.3% | 3.9% |
| Back pain | 4.6% | 3.3% | 2.5% | 2.9% |
| Rash | 1.5% | 2.5% | 2.8% | 2.7% |
| Urticaria | 0.8% | 4.7% | 1.9% | 2.3% |
| Pruritus | 3.1% | 1.7% | 2.4% | 2.3% |
| Headache | 3.8% | 3.6% | 1.1% | 1.7% |
| Nausea | 2.3% | 1.9% | 1.4% | 1.6% |
| Chest pain | 3.8% | 1.4% | 1.2% | 1.4% |
| Abdominal pain | 3.8% | 1.4% | 1.0% | 1.3% |
| Dyspnea | 0.8% | 0.6% | 1.3% | 1.2% |
| Pain | 2.3% | 2.2% | 0.8% | 1.1% |
| Diarrrhea | 2.3% | 0.8% | 0.6% | 0.7% |
| Dizziness | 2.3% | 1.4% | 0.4% | 0.7% |
| Sweating | 1.5% | 0% | 0.7% | 0.6% |
| **Overall** | **30.0%** | **17.6%** | **14.2%** | **15.8%** |

Source data: Modified from Table 12 of NDA resubmission, ISS, page 20.

***Comments:*** *Occurrence of rash, urticaria, pruritus etc. within a short period post dosing suggests that the drug might be associated with hypersensitivity reaction. This issue will be discussed under Section 6.2 because one subject in a liver trial died of a hypersensitivity reaction. It appears that dilution with slow infusion is associated with the reduction of total adverse events, and vasodilation, chest pain, abdominal pain, diarrhea, and dizziness in particular.*

6.1.2 What was seriousness of adverse events in the clinical trials?

While most of adverse events were mild and moderate, death and serious adverse events did occur in the clinical trials. In the original NDA submission, one subject died of a drug-related hypersensitivity reaction, and four subjects experienced a non-fatal serious adverse event that either was life-threatening or required hospitalization. Since the original NDA submission, there were ten patients who have subsequently died and 25 additional subjects have experienced non-fatal serious adverse events.

***Comments:*** *Our review findings are summarized as follow:*

- *Of a total of 11 death cases, one was due to a drug-related hypersensitivity reaction that will be discussed under Section 6.2. The remaining cases were judged not to be drug-related because of the patients' underlying medical conditions and the time of the events in relation to the Combidex dosing*

- *Of 29 subjects who experienced a non-fatal serious adverse event, 7 were due to drug-related hypersensitivity reactions that will be discussed under Section 6.2. There was no clear evidence that other cases were drug-related.*

## 6.2 Adverse events of special interest – immediate hypersensitivity reaction, including anaphylactic/anaphylactoid reaction

6.2.1 What is the operational definition for an immediate hypersensitivity reaction?

For the purpose of this analysis, an immediate hypersensitivity reaction is operationally defined as:

Any subjects who presented within 3 hours post Combidex administration with:
(1) one or more symptoms under Column A, OR
(2) dyspnea and any symptom under Column B (Table 6.2.1.1);

To assist in the assessment of the severity of those reactions, a term of anaphylactic/anaphylactoid reaction was used, which is operationally defined as:

> Any subjects who have an immediate hypersensitivity reaction that involves two or more body systems (Table 6.2.1.2).

**Table 6.2.1.1 Symptoms and signs used for defining an immediate hypersensitivity reaction**

| A Terms | B Terms |
|---|---|
| Urticaria | Dyspnea |
| Facial Edema/Swelling | **AND** any of the following terms: |
| Laryngeal Edema | Syncope |
| Allergic Reaction | Hypotension |
| Rash | Vasodilation/Flushing |
| Pruritus | |
| Asthma | |
| Generalized edema | |

**Table 6.2.1.2 Body system classification**

| Body System | Terms |
|---|---|
| Respiratory | Dyspnea, laryngeal edema and asthma |
| Cardiovascular | Syncope and hypotension |
| Skin | Urticaria, rash, pruritus, facial edema/swelling, vasodilation/flushing and generalized edema |

***Comments:*** *The standardization of the operational definition for hypersensitivity reactions is important for making a meaningful comparison and interpretation. Medical experts may disagree as to whether or not a particular symptom should be included in the definition. To address this issue, the distribution of each hypersensitivity symptom or sign is presented in Table 6.2.2.*

6.2.2 What were the characteristics, including severity, of subjects who had experienced an immediate hypersensitivity reaction post Combidex administration?

Of 2,061 subjects who received at least one dose, a total of 123 subjects (6%) experienced an immediate hypersensitivity reaction, including 19 subjects who developed an anaphylactic/anaphylactoid reaction per the operational definition. Table 6.2.2 shows the distribution of those subjects by demographics, symptoms, severity, reaction onset, dose and administration.

**Table 6.2.2 Distribution of subjects with an immediate hypersensitivity reaction by demographics, symptoms, severity and reaction onset**

| Demographics | Hypersensitivity Reaction (n=123) | |
|---|---|---|
| | Number | Frequency |
| Age > 65 | 16 | 13.0% |
| Female | 76 | 61.8% |
| Weight > 70 kg | 58 | 47.2% |
| History of Allergy Reaction | 19 | 15.5% |
| **Symptoms (not mutually exclusive)** | | |
| Rash | 55 | 44.7% |
| Pruritus | 49 | 39.8% |
| Urticaria | 44 | 35.8% |
| Flushing/Vasodilation | 29 | 23.6% |
| Dyspnea | 17 | 13.8% |
| Facial edema | 6 | 4.9% |
| Hypotension | 3 | 2.5% |
| Syncope | 2 | 1.6% |
| Generalized edema | 2 | 1.6% |
| Asthma | 1 | 0.8% |
| Laryngeal edema | 1 | 0.8% |
| Allergy reaction – unspecified | 1 | 0.8% |
| With 2 or more symptoms above | 62 | 50.4% |
| With 3 or more symptoms above | 23 | 18.7% |
| **Severity** | | |
| Death | 1 | 0.8% |
| Serious adverse event | 7 | 5.7% |
| Anaphylactic/anaphylactoid | 19 | 15.4% |
| Drug discontinued | 31 | 25.2% |
| Treatment needed | 68 | 55.3% |
| **Reaction onset** | | |
| < 5 minutes | 88 | 93.6% |
| **Dose and Administration** | | |
| 2.6 mg Fe/kg with 100 mL dilution | 68 | 55.3% |

The majority of the subjects who had an immediate hypersensitivity reaction were female (61.8%) and less than 65 years of age (87%). Approximately 16% of subjects had a prior history of allergic reactions.

Rash, Pruritus and urticaria were the top three presenting symptoms, followed by flushing and dyspnea. More than 50% of subjects presented with 2 or more symptoms. There was 5.7% (n=7) of hypersensitivity reactions that were considered as serious by the principle investigators, including one death, and there was 15% (n=19) of hypersensitivity reactions met the operational definition for anaphylactic/anaphylactoid reactions. More than 25% subjects had Combidex administration discontinued or 50% needed to be treated. The vast majority (93.6%) of hypersensitivity reactions occurred within 5 minutes post Combidex administration.

The subject who died of hypersensitivity reaction and 7 subjects who experienced serious hypersensitivity reactions are summarized below.

**Summary of death case:**

Patient 224/Protocol # 38,804-8A, a 70 y/o man with remote h/o colon cancer and h/o allergy to iodinated contrast, developed an anaphylactic/anaphylactoid reaction within 1-2 minutes after receiving an intravenous bolus injection of undiluted 1.1 mg/kg of Combidex given over two minutes in one of the liver imaging trials.

His first symptoms included flushing, diaphoresis, hypotension, right arm weakness, and urinary incontinence and soon he became unresponsive. Oxygen was administered on site and the emergency squad was called. The EMTs administered CPR, fluids, epinephrine and atropine in the ambulance. The patient arrived at the local emergency room in full cardiac arrest 19 minutes post-injection and was pronounced dead 35 minutes post-injection. The autopsy revealed no evidences of acute myocardial infarction or acute pulmonary embolization, and the medical examiner concluded the cause of death was cardiopulmonary arrest due to anaphylactic shock from the intravenous administration of Combidex.

His allergy history was significant for a reaction to iodinated contrast administered during a CT scan on (25 days prior to his death) in which he developed an itchy throat and a single hive on his forehead. Please refer to Appendix 7.8 for the case report form on this subject.

**Summary of subjects who experienced non-fatal serious hypersensitivity reactions**

| Patient number and protocol | Age and sex | dose | h/o contrast allergy | Symptoms | Treatment |
|---|---|---|---|---|---|
| #1508 38804-8A | 60 Female | 1.1 mg Fe/kg direct injection (undiluted) | No | facial flushing and edema followed by facial skin turning an ashen color, hypotension, headache, nausea, vomiting, left shoulder, chest, back, and abdominal pain at 5 minutes after bolus, lasting 24 hours. | IV fluids, epinephrine, diphenhydramine and hospitalization |
| #0414 38804-8B | 59 Female | 1.1 mg Fe/kg by direct injection (undiluted) | No | Facial/flushing edema, flushing of arms and legs, chills, chest pain, hypotension, unresponsiveness and hypoxia at 2 minutes | Infusion D/C'd. IV saline and epinephrine given. $O_2$ at 10 L/min via face mask given. |
| #0106 38804-5 | 23 Male | 1.7 mg Fe/kg in 100 mL saline by slow infusion | No | Dyspnea, chest pain, back pain, abdominal pain, vasodilation, hypertension, conjunctivitis, chills, diaphoresis, tachycardia at 2 minutes | Infusion D/C'd Hospitalized and D/C'd same day |
| #3003 ALS 3-15A | 65 Female | 2.6 mg Fe/kg in 100 mL saline by slow infusion | No | Cough at 5 seconds, lasting 5 minutes, dyspnea at 10 seconds, lasting 10 minutes, hypotension at 5 seconds lasting 2 minutes, vomited 90 minutes later. | Infusion D/C'd Cimetidine and dimetidin given IV |

| Patient number and protocol | Age and sex | dose | h/o contrast allergy | Symptoms | Treatment |
|---|---|---|---|---|---|
| #7026 ALS 3-31A | 63 Female | 2.6 mg Fe/kg in 100 mL saline by slow infusion | No | Flushing at 5 minutes and vasovagal faint at 15 minutes | Infusion D/C'd and no other treatment given at the time of event |
| #7227 ALS 3-31A | 42 Female | 2.6 mg Fe/kg in 100 mL saline by slow infusion | No | Dyspnea, coughing, and abdominal pain at 45 seconds. | Infusion temporarily D/C'd and then restarted and completed. IV hydrocortisone was given as well as albuterol and $O_2$ |
| #5008 ALS 3-33A | 48 Male | 2.6 mg Fe/kg in 100 mL saline by slow infusion | No | Dyspnea, sweating and flushing starting 5 seconds after start of infusion and lasting 10 minutes | Infusion D/C'd and IV methyprednisolone given. |

***Comments:*** *Occurrence of these serious hypersensitivity reactions (including death) shortly post dosing strongly suggests that these reactions are a serious drug-related problem. The death was associated with direct bolus injection in a liver imaging trial. The hypersensitivity reactions appeared to be more severe in the two other patients (Patient #1508 and #0414) that received direct bolus injection than in those subjects that received the diluted infusion.*

*The sponsor withdrew the liver-spleen imaging indication from consideration for marketing approval. The sponsor also proposed dilution with slow infusion to address the safety concern identified in the original NDA review. The focus of the discussion is the safety profile associated with dilution with slow infusion, and whether the benefit and risk ratio is favorable for the proposed indication.*

6.2.3 What are the incidence rates of hypersensitivity reactions under the proposed clinical dose and administration?

Of 2,061 subjects who received at least one dose of Combidex, 1,236 (60%) used the proposed clinical dose and administration, i.e., 2.6 mg Fe/kg diluted with 100 mL given over 30 minutes. Of 123 subjects who developed an immediate hypersensitivity reaction, 68 (55.3%) occurred with the

proposed clinical dose and method of administration. Therefore the incidence rate for immediate hypersensitivity reactions was 5.5% (68/1,236) for the proposed clinical dose and method of administration.

To assess the impact of potential underreporting on the estimate of incidence rates of hypersensitivity reactions, study-specific incidence rates were calculated for each of the studies that enrolled at least 50 subjects under the proposed clinical dose and administration (Table 6.2.3).

**Table 6.2.3 Incidence rates of immediate hypersensitivity reactions in (1) all studies and (2) in studies with more than 50 enrollees using the proposed clinical dose and administration**

| Protocol Number | Hypersensitivity Reactions | |
|---|---|---|
| | Number | Frequency |
| (1) All subjects (N=1,236) | 68 | 5.5% |
| (2) Subjects from all studies > 50 enrollees (N=840) | 49 | 5.8% |
| ALS 3-2A (N=90) | 2 | 2.2% |
| ALS 3-7A (N=56) | 0 | 0% |
| ALS 3-31A (N=306) | 25 | 8.2% |
| ALS 3-33A (N=193) | 10 | 5.2% |
| ALS 44-003A (N=195) | 12 | 6.2% |

Of the 68 hypersensitivity reactions in the subjects who received the proposed dose and method of administration, 5 were serious and 13 met the operational definition for anaphylactic/anaphylactoid reaction. Therefore the incidence rates for serious hypersensitivity reactions and anaphylactic/anaphylactoid reactions were 0.4% (5/1236) and 1.1% (13/1236) respectively.

***Comments:*** *There is no clear evidence that underreporting is a significant problem. Of 1,236 subjects who received the proposed dose and method of administration, there was no death. Serious hypersensitivity reactions and hypersensitivity reactions that met the operational definition for anaphylactic/anaphylactoid reactions were 0.4% and 1.1%, respectively.*

6.2.4 What are factors that may affect the risk of hypersensitivity reactions?

Table 6.2.4.1 shows the potential factors that may affect the incidence rates of immediate hypersensitivity reactions. The preliminary data appear to suggest that females, subjects < 65 or subjects with a prior history of allergic reactions are at a higher risk for developing hypersensitivity reactions.

**Table 6.2.4.1 Incidence rates of hypersensitivity reactions by demographics (Combidex clinical program N =2,061)**

| Demographics | Hypersensitivity Reactions | |
|---|---|---|
| | Number | Frequency |
| **Age** | | |
| < 65 (N= 1,404) | 107 | 7.6% |
| > 65 (N=651) | 16 | 2.5% |
| **Gender** | | |
| Female (N= 812) | 76 | 9.4% |
| Male (N=1,249) | 47 | 3.8% |
| **Weight (kg)** | | |
| > 70 kg (N= 1,223) | 58 | 4.7% |
| <= 70 kg (N= 834) | 65 | 7.8% |
| **History of Allergic Reaction** | | |
| No (N= 1,877) | 104 | 5.5% |
| Yes (N=184) | 19 | 10.3% |
| **US patients** | | |
| Yes (N= 874) | 58 | 6.6% |
| No (N=1,187) | 65 | 5.5% |
| **Post NDA** | | |
| Yes (N= 949) | 65 | 6.9% |
| No (N=1,112) | 58 | 5.2% |

***Comments:*** *Table 6.2.4.2 shows the impact of dose and method of drug administration on the risk of hypersensitivity reactions. Data appear to suggest that 100 mL dilution was associated with lower risk, compared to that of direct bolus inject (5.7% vs. 9.2%).*

**Table 6.2.4.2 Incidence rates of hypersensitivity reactions by dose and the method of administration**

| Dose (mg Fe/kg) | Method of Administration | | | Total |
|---|---|---|---|---|
| | Direct | 50 mL dilution | 100 mL dilution | |
| 0.3 – 1.7 | 9.3% (N=129) | 13.1% (N=38) | 6.4% (N=324) | 7.7% (N=491) |
| 2.6 | 0 (N=2) | 4.9% (N=326) | 5.5% (N=1,236) | 5.4% (N=1,564) |
| 3.4 | -- | -- | 16.7% (N=6) | 16.7% (n=7) |
| Total | 9.2% (N=131) | 5.7% (N=364) | 5.7% (N=1,566) | 6.0% (N=2,061) |

## 6.3 Immediate hypersensitivity reactions associated with other relevant drug products

6.3.1 What is the hypersensitivity reaction profile of iron-based products for a diagnostic indication?

Feridex I.V.® (ferumoxides injectable solution) is an iron oxide coated with dextran approved for intravenous (i.v.) administration as a magnetic resonance imaging contrast media. The approved clinical dose is 0.56 mg Fe/kg diluted in 100 mL saline.

In clinical trials, anaphylactic and allergic adverse events occurred in 11/2240 (0.5%) of the patients who received Feridex I.V. These events included dyspnea, other respiratory symptoms, angioedema, generalized urticaria, and hypotension; and required treatment. No deaths occurred in the clinical trials. Please refer to Product Insert (Appendix 7.9) for more information.

The Office of Drug Safety (ODS) at the FDA has reviewed the post-marketing experience associated with Feridex. No deaths have been reported since this product was approved in 1996. At this time, we do not have data on how many doses were distributed each year. Please refer to Appendix 7.10 for ODS's report.

6.3.2 What is the hypersensitivity reaction profile of iron dextran products for a therapeutic indication?

Currently there are two injectable iron dextran products approved and being marketed. These are INFeD (NDA 17-441, approved 4/29/74 [Schein Pharmaceutical]), and Dexferrum (ANDA 40-024, approved 2/23/96 [Luitpold], current owner American Regent Labs, Inc.).

IV administration of iron dextran is indicated for treatment of patients with documented iron deficiency. At this time, there is no information available from prospectively defined controlled clinical trials on the incidence of the hypersensitivity reactions associated with iron dextran use.

We have identified two articles that described the hypersensitivity reactions among two cohorts of patients who were treated with IV Iron dextran. Hamstra et al (1980) retrospectively examined the experience of 481 patients who received a total of 2,099 IV doses of iron dextran (250 or 500 mg) and found 3 life-threatening events (0.6% of patients) and 12 non-life-threatening immediate systemic reactions (2.6% of patients). These

reactions were characterized by hypotension, syncope, purpura, wheezing, dyspnea, respiratory arrest and cyanosis lasting up to one hour and occurring only after the first injection. In another report, Fishbane et al. identified 10 (1.7%) mild anaphylactoid reactions and 4 (0.7%) serious reactions in a retrospective chart review of 573 hemodialysis patients receiving iron dextran, giving a rate of about 29% of allergic reactions (characterized by any of dyspnea, wheezing, hypotension, urticaria, or angioedema) being serious. Please refer to Appendix 7.11 for more information.

Based on an ODS report (Appendix 7.10), as of December 13, 2004, FDA has received 18 cases of fatal anaphylaxis associated with the therapeutic use of iron dextran from post-marketing surveillance. There was a temporal relationship, with most patients having an onset of hypersensitivity soon after iron dextran was administered. Ten patients reacted to the test dose (2 of those patients had received iron dextran previously). Initial hypersensitivity reactions included respiratory symptoms (6), cardiovascular events (4), CNS events (3), unresponsive (2), flushing/burning (3) (not mutually exclusive); for 5 patients, the initial event was reported as anaphylaxis only. At least 5 patients had no known allergies, 3 patients had allergic reactions to drugs (including iron dextran), and 1 patient had a food allergy.

***Comments:*** *From two retrospective cohort studies, serious or life-threatening anaphylactic/anaphyactoid reactions occurred in approximately 0.6-0.7% of subjects that received the products. All of those events occurred immediately post injection and the rates are comparable to those that we have observed with the use of Combidex in clinical trials.*

## 6. 4 Summary

The key safety issue with the administration of Combidex is the risk of hypersensitivity reactions. One subject in a liver-spleen imaging trial died of an anaphylactic/anaphylactoid reaction when Combidex was administered by a direct bolus injection (a method that is no longer being proposed for marketing). There is preliminary evidence suggesting the dilution with slow infusion might reduce the incidence of hypersensitivity reactions. However, approximately 6% (n=68) of 1,236 subjects still experienced immediate hypersensitivity reactions when Combidex® was administered by the currently proposed method of administration (diluted in 100 mL saline with slow infusion over 30 minutes), including five cases which were classified as serious adverse events by the principle investigators.

Of the 1,236 subjects who received the proposed dose and method of

administration, there were no deaths. With the data, however, it is only reasonable to conclude that the risk of hypersensitivity-related death, if it occurs post Combidex administration, is not likely to be higher than approximately 1/400-500. At this time, we cannot rule out the possibility of hypersensitivity-related deaths with Combidex.

Hypersensitivity reactions occur with iron dextran products that are indicated for therapeutic purposes. There have been 18 post-marketing reports of death that were directly associated with anaphylactic/anaphylactoid reaction from the use of iron dextran products.

At this time, risk management strategies appear to be limited. We are interested in any risk management strategies that may mitigate the risk, as well as overall advice on the drug's benefit/risk ratio.