Adverse Reaction Information in the Prescribing Information

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Disclaimer

• The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.

• The labeling examples in this presentation are provided only to illustrate concepts/challenges and should not be considered FDA recommended templates.

• Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.
Learning Objectives

• Define “adverse reactions” (AR) and identify key regulatory requirements and guidance recommendations for including drug AR information in the Prescribing Information (PI)

• Discuss content/format approaches for presenting AR data in the ADVERSE REACTIONS section

• Recognize some challenges and considerations for presenting AR-related information in labeling (e.g., AR for nonindicated uses and dosages; safety claims; AR in the Highlights of PI)
Purpose of AR Information in PI

• Labeling must:
  – Contain a summary of the essential scientific information needed for the safe and effective use of the drug \(^{(21 \text{ CFR 201.56(a)(1))}}\)
  – Be informative and accurate and neither promotional in tone nor false or misleading in any particular \(^{(21 \text{ CFR 201.56(a)(2))}}\)

• In general, the ADVERSE REACTIONS section includes only information useful to health care practitioners making treatment decisions and monitoring and advising patients.\(^1\)

  ➢ Informs prescribing; patient management

\(^1\)Adverse Reactions Section Guidance
AR Regulatory Definition (21 CFR 201.57(c)(7)):

• “An undesirable effect, reasonably associated with use of a drug... that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence”

• “Does not include all adverse events observed... only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event”

• Causal relationship need not have been definitively established (see also §201.57(c)(6)(i))
Determining “some basis to believe there is a causal relationship” or “reasonably associated with use of a drug.”\textsuperscript{1}

- Based on judgment. Some factors:\textsuperscript{2}
  
  1. frequency of reporting
  2. whether AE rate for drug exceeds placebo rate
  3. extent of dose-response
  4. extent to which AE is consistent with pharmacology of the drug
  5. timing of AE relative to time of drug exposure
  6. existence of challenge and dechallenge experience
  7. whether the AE is known to be caused by related drugs

\textsuperscript{1}21 CFR 201.57(c)(7)(ii)(A); \textsuperscript{2}Adverse Reactions Section Guidance
ADVERSE REACTIONS section labeling guidance:

- AR rate “ordinarily derived from all reported AE of that type in the database used”
- Reliance on investigator-reported causality assessment discouraged
  - “Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations.”
Grouping AR Terms

AEs reported under different terms but representing the same phenomenon should ordinarily be grouped together as a single AR to avoid diluting or obscuring the true effect.¹

Table 1: Adverse Reactions in ≥ 1% of Patients with Disease-A Treated With DRUG-X (Studies 1 and 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-X N = 1306 n (%)</th>
<th>Placebo N = 300 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory infectionsᵃ</td>
<td>170 (13.0)</td>
<td>29 (9.7)</td>
</tr>
<tr>
<td>Headacheᵇ</td>
<td>46 (3.5)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Fatigueᶜ</td>
<td>33 (2.5)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Injection site reactionsᵈ</td>
<td>19 (1.5)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Tinea infectionsᵉ</td>
<td>14 (1.1)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

ᵃ Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
ᵇ Includes: headache, tension headache, sinus headache, cervicogenic headache
ᶜ Includes: fatigue, asthenia
ᵈ Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
ᵉ Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection

¹See Adverse Reactions Section Guidance
Distribution of AR Information in PI

• **ADVERSE REACTIONS** (Section 6)
• **WARNINGS AND PRECAUTIONS** (Section 5)
• **BOXED WARNING**
• **Other locations, e.g.,**¹
  – **CONTRAINDICATIONS** (Section 4)
  – Limitations of Use heading in **INDICATIONS AND USAGE** (Section 1)
  – **DRUG INTERACTIONS** (Section 7)
  – **USE IN SPECIFIC POPULATIONS** (Section 8)
  – **PATIENT COUNSELING INFORMATION** (Section 17)

¹List includes only the more frequent sections in which AR information appears; not all-inclusive
ADVERSE REACTIONS Section – Required Information and Organization
Required AR Information & Organization

Section 6 ADVERSE REACTIONS

AR listings and preceding information: ¹

- **AR** that occur with
  - the drug
  - drugs in same pharmacologically active and chemically related class, if applicable
- Information necessary to interpret the AR

Categorize AR listings by: ²

- Clinical trials experience
- Postmarketing experience
  - Listing must be separate from the listing of AR identified in clinical trials³

¹See 21 CFR 201.57(c)(7)(i); ²§ 201.57(c)(7)(ii); ³§ 201.57(c)(7)(ii)(B)

Class-related ARs/hazards often identified under Section 5 WARNINGS AND PRECAUTIONS
Clinical Trials Experience:¹

• Present AR rates of occurrence for:
  – Drug
  – Comparator (e.g., placebo)

Unless cannot be determined or presentation of comparator rates would be misleading

• If potential for misinterpretation, qualify with a disclaimer statement or footnote, e.g.,

  *The data above are not an adequate basis for comparison of adverse reaction rates between DRUG-X and Drug-Y.

  “...(e.g., if an excessive dose of an active comparator was used)”²

¹See 21 CFR 201.57(c)(7)(ii)(A); ²Adverse Reactions Section Guidance
**Presenting AR for Drug and Comparator Safety Claim vs. Data Display**

**Restrictions for Safety Claims**

(require substantiation of claim)

**Requirement to Provide Drug/Comparator AR from Clinical Trials**

(serves informational purpose)

For comparisons of ARs between drugs:¹

- *(Drug products)* Any claim comparing the drug with other drugs in terms of frequency, severity, or character of ARs must be based on adequate and well-controlled studies (as defined in 21 CFR 314.126(b))³

- *(Biological products)* Any such claim must be based on substantial evidence

**Clinical Trials Experience:**²

- The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading

¹See 21 CFR 201.57(c)(7)(iii); ²§ 201.57(c)(7)(ii)(A); ³unless this requirement is waived under § 201.58 or § 314.126(c)
Information Preceding AR Presentation

- AR listing(s) must be preceded by the information necessary to interpret the ARs, e.g., for clinical trials\(^1\)
  - Total number exposed
  - Extent and nature of exposure

- Also include:
  - Demographics
  - Disease severity/characteristics

- Identify important exclusions from safety database

\(^1\)See 21 CFR 201.57(c)(7)(i)
6.1 Clinical Trials Experience

The DRUG-X safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with DRUG-X 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

DRUG-X was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with DRUG-X at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy.

Patients with unstable cardiac disease, narrow-angle glaucoma, symptomatic prostatic hypertrophy, and/or bladder outlet obstruction were excluded from these trials.
Disclaimer – AR Rates Not Comparable Across Trials

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice.

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for DRUG-X and at Least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-X 120 mg Monthly N=705, %</th>
<th>Placebo Monthly N=1451, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for Either Dosing Regimen of DRUG-Y and at Least 2% Greater than Placebo (up to 3 Months of Treatment) in Studies 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-Y 225 mg Monthly N=290, %</th>
<th>DRUG-Y 675 mg Quarterly N=667, %</th>
<th>Placebo Monthly N=668, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>43</td>
<td>45</td>
<td>38</td>
</tr>
</tbody>
</table>

E.g., from 2 different labeling, AR rates across trials should not be compared.
AR Listings – Selecting AR Rate Cut-Offs and Considerations for Data Display
AR Listings—Selecting AR Rate Cut-Offs

Section 6 ADVERSE REACTIONS

- Must describe the overall AR profile of the drug based on the entire safety database\(^1\)
- Must list the AR identified in clinical trials that occurred at or above a specified rate appropriate to the safety database\(^2\)

- Would be expected to vary between drugs and between indications of a drug
- Factors, e.g.,\(^3\)
  - Size of safety database
  - Designs of the trials in database
  - Disease/condition

- Cut-off should be noted in the listing/table header, accompanying text, or footnote.\(^3\)
- Denominator should be provided (N = number of patients) for each column in a table/listing\(^4\)

\(^1\)21 CFR 201.57(c)(7); \(^2\) § 201.57(c)(7)(ii)(A); \(^3\)Adverse Reactions Section Guidance; \(^4\)Except for ARs identified from postmarketing spontaneous reports
## AR Listings—Considerations for Data Display

### Section 6 ADVERSE REACTIONS

Consider AR Rate of Drug Relative to Comparator

<table>
<thead>
<tr>
<th>Include AR in listing when AR rate: Drug &gt; Placebo</th>
<th>If Drug ≤ Placebo, omit from AR listing...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unless a suspected AR:</strong></td>
<td></td>
</tr>
<tr>
<td>• There is some compelling factor (e.g., timing)</td>
<td></td>
</tr>
<tr>
<td>that suggests the event is caused by drug</td>
<td></td>
</tr>
<tr>
<td>• Such AR (where rate of drug ≤ placebo) should</td>
<td></td>
</tr>
<tr>
<td>be discussed in commentary (i.e., presented</td>
<td></td>
</tr>
<tr>
<td>as text)</td>
<td></td>
</tr>
</tbody>
</table>

1See Adverse Reactions Section Guidance
### AR Listings—Considerations for Data Display

**Section 6 ADVERSE REACTIONS**

<table>
<thead>
<tr>
<th>Include AR in listing when AR rate:</th>
<th>If Drug ≤ Placebo, omit from AR listing...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug &gt; Placebo</td>
<td>Unless a suspected AR</td>
</tr>
</tbody>
</table>

- Above approach does not account for chance findings in either direction
- **If active comparator, the above may not apply; choose appropriate rate**
  - E.g., May be different considerations if DRUG-X is indicated as monotherapy vs. in combination with Drug-Y and the comparator is Drug-Y
- Statistical significance testing should be omitted if not based on a prespecified hypothesis in an adequately designed and powered study.¹,²

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¹See Adverse Reactions Section Guidance; ²21 CFR 201.57(c)(7)(iii)
Table 1: Adverse Reactions in 5% or More of DRUG-X-Treated Patients With Disease-A in Studies 1 and 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>DRUG-X N=1029, %</th>
<th>Placebo N=1028, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- Exclude AE with rate of drug ≤ placebo
  - Remove from AR listing/table
  - If suspected AR, discuss separately in commentary outside of AR table
### Table 2: Adverse Reactions in >10% of DRUG-X-Treated Group and ≥5% Greater Than in Control-Treated Group in Patients With Disease-A

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-X (N=45)</th>
<th>Control (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades, %</td>
<td>Grade ≥3, %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49</td>
<td>42</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>Anemia</td>
<td>47</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>38</td>
<td>4.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>13</td>
<td>2.2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>11</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Categorize/order AR within a listing:

By body system, severity of AR, or in order of decreasing frequency (or by a combination of these), as appropriate (CFR 201.57(c)(7)(ii))
# Laboratory AR

## Table 4: Laboratory Abnormalities Reported in ≥ 10% (All Grade) or ≥ 5% (Grade 3–4) of Patients with Disease-A in Study 1

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>DRUG-X 8 mg daily (N=86)</th>
<th>All Grades (%)</th>
<th>Grade 3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>35</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Leukocytes decreased</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate increased</td>
<td>76</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>52</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>40</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>41</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>41</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>37</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>30</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Magnesium decreased</td>
<td>30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Phosphate decreased</td>
<td>24</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Calcium increased</td>
<td>22</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Potassium increased</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Adverse Reaction</td>
<td>Study 1 Placebo (N = 3576) n (%)</td>
<td>Study 1 DRUG-X (N = 3581) n (%)</td>
<td>Study 2 Comparator (N = 2014) n (%)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>434 (12.1)</td>
<td>468 (13.1)</td>
<td>194 (9.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>208 (5.8)</td>
<td>235 (6.6)</td>
<td>110 (5.5)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>140 (3.9)</td>
<td>163 (4.6)</td>
<td>81 (4.0)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>67 (1.9)</td>
<td>86 (2.4)</td>
<td>38 (1.9)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>79 (2.2)</td>
<td>84 (2.3)</td>
<td>53 (2.6)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>54 (1.5)</td>
<td>80 (2.2)</td>
<td>42 (2.1)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>68 (1.9)</td>
<td>72 (2.0)</td>
<td>36 (1.8)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>62 (1.7)</td>
<td>72 (2.0)</td>
<td>34 (1.7)</td>
</tr>
</tbody>
</table>

The listing of common ARs should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative.

1See Adverse Reactions Section Guidance
Subgroup AR Information and AR for Multiple Indications
Presenting AR When There Are Multiple Indications

6.1 Clinical Trials Experience

**Migraine**

The safety of DRUG-X was evaluated in 2586 patients with migraine who received at least one dose of DRUG-X, representing 1487 patient-years of exposure. Of these, 1290 patients were exposed for 6 months and 526 patients were exposed for 12 months.

In placebo-controlled clinical studies (Studies 1, 2, and 3), 705 patients received at least one dose of DRUG-X 120 mg once monthly, and 1451 patients received placebo, during 3 months of double-blind treatment. Of the DRUG-X-treated patients, approximately 85% were female, 77% were white, and the mean age was 41 years at study entry.

The most common adverse reaction was injection site reactions that occurred within up to 6 months of treatment in the migraine studies.

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for DRUG-X and at least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2, and 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-X 120 mg Monthly N=705, %</th>
<th>Placebo Monthly N=1451, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>18</td>
<td>13</td>
</tr>
</tbody>
</table>

**Episodic Cluster Headache**

DRUG-X was studied for up to 2 months in a placebo-controlled trial in patients with episodic cluster headache (Study 4) [see Clinical Studies (14.2)]. A total of 106 patients were studied (49 on DRUG-X and 57 on placebo). Of the DRUG-X-treated patients, approximately 84% were male, 88% were white, and the mean age was 47 years at study entry...

Overall, the safety profile observed in patients with episodic cluster headache treated with DRUG-X 300 mg monthly was consistent with the safety profile in migraine patients.
Multiple Indications

- A single AR table may be adequate
- Use > 1 AR table if there are substantial, clinically important differences between indications
  - Consider, if appropriate, focusing additional tables on ARs with rate differences
- Text should summarize any important differences/similarities in AR profiles among indications
- Same concept applies when there are different:
  - Demographic subgroups
  - Dosage forms
  - Dosing regimens
  - Study durations
  - Types of studies (e.g., intensely monitored small studies vs. a large outcome study)
AR in Subgroups (e.g., Renal Impairment)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Adverse Reactions in Patients with Renal Impairment

In Studies 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In DRUG-X-treated patients with renal impairment, diarrhea, including severe diarrhea, was reported at a numerically higher frequency than in DRUG-X-treated patients with normal renal function (Table 2).

Table 2: Diarrhea (Including Severe Diarrhea) in DRUG-X-Treated Patients With Renal Impairment (Study 1 and 2)

<table>
<thead>
<tr>
<th></th>
<th>DRUG-X % (n/N)</th>
<th>Placebo % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with renal impairment</td>
<td>20% (39/194)</td>
<td>0.6% (1/174)</td>
</tr>
<tr>
<td>Patients with normal renal function</td>
<td>13% (53/407)</td>
<td>3.5% (15/426)</td>
</tr>
</tbody>
</table>

1See 21 CFR 201.57(c)(7)(ii)(A); 2Adverse Reactions Section Guidance
Subgroups – Gender-Specific AR

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

A total of 1064 subjects and 1069 subjects with moderate to severe condition -X were treated with DRUG-X and placebo, respectively, for 12 weeks in 3 controlled clinical trials. The only adverse drug reaction that was reported in at least 1% of subjects was nausea, DRUG-X (3%) versus placebo (2%).

The following additional adverse reactions occurred in female DRUG-X-treated subjects: vulvovaginal mycotic infection (0.8%) and vulvovaginal candidiasis (0.7%).

14 CLINICAL STUDIES

Efficacy was assessed in a total of 2002 subjects 9 years of age and older. Overall, 57% were female, 78% were Caucasian, 15% were Black or African American and 51% were adults (18 to 45 years of age)...

Rates for gender-specific AR should be determined using appropriate denominator, and that denominator should be identified in a footnote. Consider including subgroup denominator: 0.8% (5/606) 0.7% (4/606)

1See Adverse Reactions Section Guidance
ADVERSE REACTIONS Section – Other Requirements and Topics
AR With Significant Clinical Implications
Section 6 ADVERSE REACTIONS

Clinical Trials Experience: ¹

• For AR with significant clinical implications, the listings must be supplemented with additional detail (if data are available and important):
  – Nature, frequency, and severity of the AR
  – Relationship of the AR to drug dose and demographic characteristics

¹See 21 CFR 201.57(c)(7)(ii)(A)
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience

**Dose-Dependent Adverse Reactions**

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of DRUG-X to placebo, the following adverse reactions were dose-related: headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth.

<table>
<thead>
<tr>
<th></th>
<th>Placebo N = 226 (%)</th>
<th>DRUG-X 37.5 mg N = 58 (%)</th>
<th>DRUG-X 75 mg N = 120 (%)</th>
<th>DRUG-X 150 mg N = 218 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8</td>
<td>7</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
### Separate Listing of Less Common AR

Table 2: Adverse Reactions Reported in greater than or equal to 1% of Patients with Disease-A Treated with DRUG-X 15 mg in Placebo-controlled Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo n=1042, %</th>
<th>DRUG-X 15 mg n=1035, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection (URTI)*</td>
<td>9.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Cough</td>
<td>1.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the DRUG-X 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing (CFR 201.57(c)(7)(ii)(A))
Long-Term Extension Study (Uncontrolled) Data

• Include data if shows new AR or more severe/frequent AR
• Omit overstatements/unsubstantiated claims about similar long-term safety compared to controlled period if based solely on uncontrolled long-term extension study data

The most common adverse reactions (≥10%) that occurred in DRUG-X-treated patients in the long-term extension to Study 1 that did not occur in the 3-month placebo-controlled trials were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).
Adverse Reactions Heading in the Highlights of Prescribing Information
Highlights vs. Section 6 – AR Rate Cut-Offs

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Table 4: Adverse Reactions (≥ 10%) in Patients Receiving DRUG-X in Studies 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Highlights (Adverse Reactions Heading):

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, paresthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, paresthesia, arthralgia, and vision disorders. (6.1)

A list of the most frequently occurring AR... along with the criteria used to determine inclusion (e.g., incidence rate) (CFR 201.57(a)(11))
AR in Highlights – Consider Whether to Include Laboratory AR

6.1 Clinical Trials Experience

... The most common adverse reactions (reported in ≥20%) were diarrhea, nausea, anemia, and vomiting. Tables 3 and 4 summarize the common adverse reactions and laboratory abnormalities, respectively, in Study 1 during randomized treatment.

Table 3: Adverse Reactions Reported in ≥5% Patients With Disease-X Receiving DRUG-X 400 mg With a Difference Between Arms of >5%

Table 4: Selected Laboratory Abnormalities That Have Worsened from Baseline (≥20%) in Patients With Disease-X Receiving DRUG-X With a Difference Between Arms of >10%

Highlights:

The most common adverse reactions (≥20%) are diarrhea, nausea, anemia, and vomiting (6.1).

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.¹

¹See Adverse Reactions Section Guidance
AR (Laboratory and Nonlaboratory) in Highlights

Decide whether to list laboratory ARs separately (e.g., if using different cut-offs in Highlights)

---ADVERSE REACTIONS---

- **Most common adverse reactions (incidence ≥ 30%)** are capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia and weight increase.
- **Most common laboratory abnormalities (incidence ≥ 50%)** are decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT and AST. (6.1)

AR listing (Table 3) cut-off in Section 6 is ≥ 10%*

Laboratory AR listing (Table 4) cut-off in Section 6 is ≥ 10%*

*In the example illustrated
ARs (Laboratory and Nonlaboratory) in Highlights

Example of single, merged (nonlaboratory and laboratory) AR listing:

Most common adverse reactions, **including laboratory abnormalities (all grades, incidence ≥ 20%)**, were:

- glucose increased
- creatinine increased
- diarrhea
- rash
- lymphocyte count decreased
- GGT increased
- nausea
- ALT increased
- fatigue
- hemoglobin decreased
- lipase increased
- decreased appetite
- stomatitis
- vomiting
- weight decreased
- calcium decreased
- aPTT prolonged
- alopecia (6.1)
ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are:

- **DRUG-X Injection**: administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache. (6.1)
- **DRUG-X Tablets**: diarrhea, nausea, vomiting, hepatic enzyme elevation. (6.1)

*See 21 CFR 201.57(d)(4)*
AR Information in Section 6 vs. 14
Where Should AR-Related Information Go???

Sections 6 and 14 – Regulations and Guidance

6 ADVERSE REACTIONS

- AR data (drug AR/risk)
  - Overall AR profile of drug based on entire safety database
  - Ordinarily, AR is described in the ADVERSE REACTIONS section
- Cross-reference Section 14 for detailed study discussion

14 CLINICAL STUDIES

- “Any detailed discussion of the study...”
- “Details of studies that...basis for comparative safety claims would ordinarily be discussed in the CLINICAL STUDIES section”
- “Cross-reference Section 14 for AR data...”
- “Any discussion...that relates to a risk from the use of the drug must also refer to the other sections of labeling where the risk is identified...”
- “Clinical studies that prospectively evaluate an important safety endpoint...” should usually be included in the CLINICAL STUDIES section
- “The section should also include safety data from controlled studies specifically designed to evaluate a safety endpoint...”
- “…in some cases it may be appropriate to present important information about safety in the CLINICAL STUDIES section (e.g., if the safety data are best understood when presented with a detailed study description or in the context of effectiveness results).”
- “If safety data are presented in the CLINICAL STUDIES section, they...”

1 See 21 CFR 201.57(c)(7); 2 § 201.57(c)(15); 3 § 201.57(c)(15)(ii); 4 Adverse Reactions Section Guidance; 5 guidance Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products– Content and Format (Jan 2006)
Choosing Best Location of AR-Related Information—Section 6 vs 14

For prospectively evaluated/pre-specified safety endpoint(s)

➢ Determine best location based on overall clinical message (depends on study findings)

Where is a prescriber likely to look for the safety information? Consider, e.g.,

6 ADVERSE REACTIONS

➢ AR data (drug AR/risk) (e.g., drug demonstrates lower AR rate than active comparator, but still an AR of the drug)
  – Include appropriate statistical testing results (e.g., p-value, confidence intervals) with data presentation, as appropriate

➢ Cross reference Section 14 for detailed study description

➢ Safety data with unclear clinical impact

14 CLINICAL STUDIES

➢ Detailed study description
  Cross-reference Section 6 for AR data

➢ Study results that demonstrate clinical benefit or absence of AR
6.1 Clinical Trials Experience

The mean duration of exposure to DRUG-X was 154 days and to enoxaparin/warfarin was 152 days in the Study 1. Adverse reactions related to bleeding occurred in 417 (15.6%) DRUG-X treated patients compared to 661 (24.6%) enoxaparin/warfarin treated patients. The discontinuation rate due to bleeding events was 0.7% in the DRUG-X treated patients compared to 1.7% in enoxaparin/warfarin treated patients in Study 1.

In Study 1, DRUG-X was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from Study 1 are summarized in Table 5.

---

Table 5: Bleeding During the Treatment Period in Patients with Condition-A (Study 1)

<table>
<thead>
<tr>
<th></th>
<th>DRUG-X</th>
<th>Enoxaparin/Warfarin</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2876</td>
<td>N=2689</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>15 (0.6)</td>
<td>49 (1.8)</td>
<td>0.31 (0.17, 0.55), p&lt;0.0001</td>
</tr>
<tr>
<td>CRNM*</td>
<td>103 (3.9)</td>
<td>215 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Major + CRNM</td>
<td>115 (4.3)</td>
<td>261 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>313 (11.7)</td>
<td>505 (18.8)</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>402 (15.0)</td>
<td>676 (25.1)</td>
<td></td>
</tr>
</tbody>
</table>

* CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.
6.1 Clinical Trials Experience

**Neuropsychiatric Adverse Reactions**

For Study 1, the analysis of subjects with neuropsychiatric adverse reactions by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse reactions was 24% and 57% in the DRUG-X and Drug-Y groups, respectively.

A statistically significantly lower proportion of DRUG-X-treated subjects compared to Drug-Y-treated subjects reported neuropsychiatric adverse reactions by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

**Table 2: Neuropsychiatric Adverse Reactions in Patients With Disease-A (Study 1, Week 48)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRUG-X N=364</th>
<th>DRUG-Y N=364</th>
<th>Treatment Difference (DRUG-X — Drug-Y) Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep disorders and disturbances‡</td>
<td>12%</td>
<td>26%</td>
<td>-13.3 (-19.1, -7.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>37%</td>
<td>-28.3 (-34.0, -22.5)</td>
</tr>
<tr>
<td>Altered sensorium§</td>
<td>4%</td>
<td>8%</td>
<td>-3.8 (-7.6, -0.3)</td>
</tr>
</tbody>
</table>

* All causality and all grade events were included in the analysis.
† The 95% CIs were calculated using Miettinen and Nurminen’s method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.001).
1 INDICATIONS AND USAGE

DRUG-X is indicated:

• as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus,

• to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease [see Clinical Studies (14.3)].

Limitations of Use:
The use of DRUG-X is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis because it would not be effective in these settings.
Study 1 (NCT01234567) was a multi-national, multi-center, placebo-controlled, double-blind trial that enrolled N patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Patients eligible to enter the trial were...

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferiority was demonstrated. Type 1 error was controlled across multiple tests.

DRUG-X significantly reduced the occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.87 (0.78, 0.97)...

Figure 5 Kaplan-Meier: Time to First Occurrence of a MACE in Study 1 (Patients with T2DM and Atherosclerotic CVD)
Postmarketing Observational Study Data

• If presented in *Postmarketing Experience* subsection, consider headings:

  6.1 Clinical Trials Experience
  6.2 Postmarketing Experience
  Adverse Reactions from Observational Studies
  Adverse Reactions from Postmarketing Spontaneous Reports

• AR categorization – **Based on type of data**, rather than timing/source of data

• Spontaneous reports\(^2\) (under *Postmarketing Experience*) incorporates voluntary, unsolicited ARs (outside of clinical study context) reported by/in:
  – Patients, caregivers
  – Health care providers
  – Application holders
  – FAERS
  – Published literature
Presenting AR Information for Nonindicated Uses or Dosages
Importance of Conveying Clinically Significant AR/Risk Information

• Ordinarily, information in PI must be for approved indications/dosages
  — Indications or uses must not be implied or suggested in other sections of the labeling if not included in (INDICATIONS AND USAGE) section\(^1\)
  — Dosing regimens must not be implied or suggested in other sections of the labeling if not included in (DOSAGE AND ADMINISTRATION) section\(^2\)

• Some exceptions, e.g.,
  — When there are important ARs/risks for a commonly prescribed unapproved use\(^3\)
  — When the AR/safety profile of an approved use relied on AR data from other studied but unapproved uses

• When presenting AR data for unapproved uses, include disclaimer if needed (statement that the drug is not approved for those uses/dosages)

\(^1\)See 21 CFR 201.57(c)(2)(iv) and (v); \(^2\) § 201.57(c)(3)(ii); \(^3\) § 201.57(c)(6)(i); see also § 201.57(c)(15)(i); and § 201.56(a)(3)
WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- DRUG-X is contraindicated in patients less than 6 years of age. In nonclinical studies in young juvenile rats, administration of drug-x caused deaths presumed to be due to dehydration [see Contraindications, Use in Specific Populations (8.4)].
- Avoid use of DRUG-X in patients 6 years to less than 12 years of age [see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].
- The safety and effectiveness of DRUG-X have not been established in patients less than 18 years of age [see Use in Specific Populations (8.4)].
ARs for Nonindicated Dosages Within Pooled Safety Data

6.1 Clinical Trials Experience

The safety of DRUG-X was evaluated in 208 adult and pediatric patients 5 years of age and older in 6 clinical trials for the treatment of disease-X; 186 patients received a single dose of 10 mg/kg/day and 28 patients received 20 mg/kg/day. The 10 mg/kg/day dosing regimen is not approved [see Dosage and Administration (2)]. Pooled data for adverse reactions reported in 2% or more of the patients in these clinical trials are presented in Table 1.

Table 1: Adverse Reactions Occurring in >2% of Patients Who Received a Total of 10 mg/kg or 20 mg/kg DRUG-X for Disease-X Treatment (Pooled across 6 studies)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>DRUG-X (10 mg/kg/day or 20 mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>58</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>23</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Vertigo</td>
<td>8</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
</tr>
<tr>
<td>Urticaria</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
</tr>
</tbody>
</table>

Include a disclaimer statement for the nonindicated dosage if necessary to present its AR.
ARs for Nonindicated Uses Within Pooled Safety Data

1 INDICATIONS AND USAGE

Drug-X is indicated for the treatment of adults with Cancer type C.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

... The safety of DRUG-X was assessed in a single-arm clinical trial that included 280 adults with Cancer types A, B, and C (60 adults had Cancer type C).

Disclaimer not needed if drug indication is clear (e.g., if the pooled presentation of AR is not likely misunderstood as approved population
Summary

• Labeling regulations identify, generally, the AR information that must be contained in the ADVERSE REACTIONS section of the PI and how to categorize it.

• Clinical judgment is needed to determine what data to include and how to present it.
  – E.g., choosing data cut-offs; whether to present ARs for nonindicated uses/dosages.

• Consider the overall clinical message when deciding upon location and presentation of AR information in labeling.
  – E.g., ADVERSE REACTIONS vs. CLINICAL STUDIES section; use of qualifiers/disclaimers, if appropriate.

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Challenge Question 1

For adverse reactions (AR) with significant clinical implications, AR listing(s) must be supplemented with information on which of the following:

a) Nature, frequency, and severity of the AR

b) Relationship of the AR to drug dose

c) Relationship of the AR to demographic characteristics

d) All of the above, if data are available and important
Selected Regulatory References

- Statute: Food, Drug, & Cosmetic Act (FD&C Act)
- Regulations: 21 CFR 201.57(c)(7), (6), (1), (15); (a)(11), (10), (4)
- Guidance for Industry:
  - *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Jan 2006)
  - *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Oct 2011)
  - *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Jan 2006)
  - *Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements* (Feb 2013)
Backup Slides
Where Should AR-Related Information Go???
Sections 6 and 14 – Regulations and Guidance

**6 ADVERSE REACTIONS**

- **AR data (drug AR/risk)**
  - Overall AR profile of drug based on entire safety database\(^1\)
  - Ordinarily, safety data are described in the ADVERSE REACTIONS section\(^5\)

- **Cross reference Section 14 for detailed study discussion\(^2\)**

- **“A negative finding can be reported** if the absence of the reaction is convincingly demonstrated in a trial of adequate design and power”\(^4\)

**14 CLINICAL STUDIES**

- **“Any detailed discussion of the study”\(^2\)**
  - “Details of studies that are the basis for comparative safety claims would ordinarily be discussed in the CLINICAL STUDIES section”\(^4\)

- **Cross-reference Section 6 for AR data**
  - “Any discussion... that relates to a risk from the use of the drug must also refer to the other sections of labeling where the risk is identified or discussed”\(^3\)

- **Sometimes, AR/safety data can be in CLINICAL STUDIES section**
  - “Clinical studies that prospectively evaluate an important safety endpoint”... “should usually be included in the CLINICAL STUDIES section”\(^5\)
  - “The section should also include safety data from controlled studies specifically designed to evaluate a safety endpoint”\(^5\)
  - “...in some cases it may be appropriate to present important information about safety in the CLINICAL STUDIES section (e.g., if the safety data are best understood when presented with a detailed study description or in the context of effectiveness results).”\(^5\)

  “If safety data are presented in the CLINICAL STUDIES section, they must be cross-referenced in the ADVERSE REACTIONS section and other sections, as appropriate (21 CFR 201.57(c)(15)(ii)).”\(^5\)

\(^1\)See 21 CFR 201.57(c)(7); \(^2\) § 201.57(c)(15); \(^3\) § 201.57(c)(15)(ii); \(^4\) guidance Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products—Content and Format (Jan 2006); \(^5\) guidance Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format (Jan 2006)