Regulatory Education for Industry (REdI): PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES

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Challenges and Issues With the DOSAGE AND ADMINISTRATION Section of Labeling

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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 fictitious and are provided only to demonstrate current labeling development challenges.

DOSAGE AND ADMINISTRATION (D&A) Section: Resources

Code of Federal Regulations:

- 21 CFR 201.57(c)(3)

Guidance:

- D&A Section of Labeling Guidance

Best Labeling Practice:

- Institute for Safe Medication Practices' List of Error-Prone Abbreviations, Symbols, and Dose Designations

D&A Section #1: What can be Improved?

2 DOSAGE AND ADMINISTRATION

It is recommended that DRUGOXIDE be administered with food. DRUGOXIDE should be given once daily.

2.1 General Dosing Recommendations

Administer 50 mg of DRUGOXIDE to adults and administer 25 mg to pediatric patients between 12 and 17 years old. If adult patients have mild renal impairment administer 40 mg; if adult patients have moderate renal impairment administer 30 mg; and if adult patients have severe renal impairment administer 20 mg.

If pediatric patients have mild renal impairment administer 15 mg; if pediatric patients have moderate renal impairment administer 10 mg; and if pediatric patients have severe renal impairment, administer 5 mg.

D&A Section #1: Improved Language

2 DOSAGE AND ADMINISTRATION

Administer DRUGOXIDE once daily with food. Table 1 displays the recommended dosage of DRUGOXIDE in adults and pediatric patients between 12 and 17 years old.

Table 1: Recommended DRUGOXIDE Dosage (Administered Once Daily) in Adults and Pediatric Patients Between 12 and 17 Years Old

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
Estimated GFR*	greater than 90 mL/minute	60-90 mL/minute	30-60 mL/minute	less than 30 mL/minute
Adults	50 mg	40 mg	30 mg	20 mg
Pediatric Patients Between 12 and 17 Years Old	25 mg	15 mg	10 mg	5 mg

* Estimated glomerular filtration rate (GFR) by Cockcroft-Gault

D&A Section Example #1: Comments

- For all FPI sections, when a subsection heading is used, capture all information under a subsection heading
  - Avoid including information between Section 2 and subsection 2.1
  - This does not apply when listing clinically significant adverse reactions between Section 6 (ADVERSE REACTIONS) and subsection 6.1 (Clinical Trials Experience)
  - In electronic world, may miss this "floating" information

- Recommend command language

- Tables can improve clarity of complex dosage instructions*

- All table titles should include study population, should represent information in table, and should be in title case**

* Section III(B) - D&A Section of Labeling Guidance

** Appendix C - Clinical Studies Section of Labeling Guidance

D&A Section: Example #2

What Can Be Improved?
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dosage** Administer 40 mg of DRUGOXIDE oral solution orally every 12 hours. If DRUGOXIDE is administered intravenously, clinically significant hypotension may occur which may require fluids and pressor agents.
Improved Language
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dosage** Administer 40 mg of DRUGOXIDE oral solution orally every 12 hours. Avoid intravenous administration *[see Warnings and Precautions (5.3)]*. **5 WARNINGS AND PRECAUTIONS** **5.3 Hypotension with Inappropriate Administration** Cases of clinically significant hypotension occurred with inappropriate administration of DRUGOXIDE oral solution intravenously. Some cases required fluids and pressor agents. Administer DRUGOXIDE oral solution only by the oral route and avoid intravenous administration of DRUGOXIDE.

D&A Section Example #2: Comments

- Clinically significant adverse reactions should be in WARNINGS AND PRECAUTIONS section*
- Ordinarily information in another section should be discussed in D&A if specific implications for dosing or administering a drug**
- Dosing regimens must not be implied or suggested if not include in D&A section***

* 21 CFR 201.57(c)(6) and W&P, Contraindications, and BW Sections of Labeling Guidance
** Section IV - D&A Section of Labeling Guidance
*** 21 CFR 201.57(c)(3)(ii), 21 CFR 201.56(a)(3)

D&A Section: Example #3

What Can Be Improved?

2 DOSAGE AND ADMINISTRATION

2.3 Drug Interactions

Administration of DRUGOXIDE with moderate CYP3A4 inhibitors results in a 95% and 87% increase in the AUC and Cmax of drugoxide, respectively, compared to administration of DRUGOXIDE alone. No dosage adjustments are needed with concomitant use of DRUGOXIDE with moderate CYP3A4 inhibitors.

Administration of DRUGOXIDE with strong CYP3A4 inhibitors results in a 205% and 185% increase in AUC and Cmax of drugoxide, respectively, compared to administration of DRUG-X alone. With concomitant administration of DRUGOXIDE with strong CYP3A4 inhibitors, decrease the dosage by 50%.

Improved Language

2 DOSAGE AND ADMINISTRATION

2.3 Dosage Adjustment with Strong CYP3A4 Inhibitors

With the concomitant use of DRUGOXIDE with strong CYP3A4 inhibitors decrease the DRUGOXIDE dosage to 30 mg once daily *[see Drug Interactions (7.3)]*. No dosage adjustment is needed for moderate CYP3A4 inhibitors.

D&A Section: Example #3: Comments

- D&A section should ordinarily:*
  - Include drug interaction (DI) information if specific implications for dosing or administering a drug
  - Be limited to recommended dosage modification due to DI; omitting discussion of DI mechanism, study findings, or other DI details
- Provide actual modified dosage (i.e., 30 mg once daily) rather than percentage (i.e., 50%) by which dosage should be adjusted
- Subsection heading should be consistent with information in body of subsection
  - Heading should be specific

* 21 CFR 201.57(c)(3)(i)(H); Section IV - D&A Section of Labeling Guidance

D&A Section: Example #4

What Can Be Improved?

2 DOSAGE AND ADMINISTRATION

2.3 Severe Renal Impairment

Patients with severe renal impairment had increased exposure to drugoxide compared to patients with normal renal function. Patients with severe renal impairment should be monitored for clinically significant adverse reactions because there is a possibility of cumulative effects in such patients *[see Use in Specific Populations (8.7)]*.

2.4 Geriatric Patients

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range *[see Use in Specific Populations (8.5)]*.

Improved Language

2 DOSAGE AND ADMINISTRATION

2.3 Severe Renal Impairment

Patients with severe renal impairment had increased exposure to drugoxide compared to patients with normal renal function. Patients with severe renal impairment should be monitored for clinically significant adverse reactions because there is a possibility of cumulative effects in such patients *[see Use in Specific Populations (8.7)]*.

2.4 Geriatric Patients

Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range *[see Use in Specific Populations (8.5)]*.

D&A Section Example #4: Comments

- Ordinarily information in another section should be discussed in D&A if specific implications for dosing or administering a drug*
- Dosage adjustments in patients with renal impairment must be in D&A section**
- If clinical implications for differences in response in patients with renal impairment compared to patients with normal renal function include in USE IN SPECIFIC POPULATIONS section***

* Section IV - D&A Section of Labeling Guidance

** 21 CFR 201.57(c)(3)(i)(H)

*** Section VI - Pharmacokinetics in Patients with Impaired Renal Function Guidance

D&A Section: Example #5

What Can Be Improved?

2 DOSAGE AND ADMINISTRATION
2.4 Monitoring
During treatment with DRUGOXIDE:

- Obtain neutrophil count because DRUGOXIDE there have been cases of neutropenia with DRUGOXIDE use
- Assess tuberculosis risk factors because DRUGOXIDE is an immunosuppressant and there have been cases of tuberculosis in high risk patients
- Ensure patients are up to date with all recommended non-live immunizations prior to starting DRUGOXIDE.

Improved Language

2 DOSAGE AND ADMINISTRATION
2.4 Testing, Evaluation, and Immunizations Prior to DRUGOXIDE Administration
Prior to treatment with DRUGOXIDE:

- Obtain neutrophil count *[see Warnings and Precautions (5.4)]*
- Assess for tuberculosis risk factors *[see Warnings and Precautions (5.5)]*
- Ensure patients are up to date with all recommended non-live immunizations *[see Warnings and Precautions (5.8)]*.

For severe neutropenia, adjust dosage …

D&A Section: Example #5: Comments

- Should identify any safety monitoring procedures that should be implemented before initiating or during therapy to determine how to **administer drug** (e.g., stop drug, adjust dosage, delay additional course)*
- D&A section should cross-reference discussion of safety concern in WARNINGS AND PRECAUTIONS section*
  - D&A section should contain actionable information; whereas, the "why" should be in other sections
- Must include steps that should be taken to prevent or mitigate clinically significant adverse reactions in W&P section**

* Section II(C) - D&A Section of Labeling Guidance

** 21 CFR 201.57(c)(6)

D&A Section: Example #6

What Can Be Improved?
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dosage** The recommended DRUGOXIDE dosage for the acute treatment of a migraine is 10 mg after a migraine occurs. DRUGOXIDE has been shown to reduce symptoms of migraine within 2 hours of administration. The maximum recommended DRUGOXIDE dosage is 20 mg within a 24 hour period.
Option #1: Improved Language
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dosage** Administer 10 mg of DRUGOXIDE after a migraine occurs. If there is no significant response 2 hours after administration, administer an additional 10 mg of DRUGOXIDE. The maximum recommended DRUGOXIDE dosage is 20 mg within a 24 hour period.
Option #2: Improved Language
2 DOSAGE AND ADMINISTRATION **2.1 Recommended Dosage** Administer 10 mg of DRUGOXIDE after a migraine occurs. The maximum recommended DRUGOXIDE dosage is 20 mg within a 24 hour period. **14 CLINICAL STUDIES** **14.1 Acute Migraines** In Study 1, DRUGOXIDE reduced symptoms of migraine within 2 hours of administration (see Table 4).

D&A Section Example #6: Comments

- Clinical study results should be in CLINICAL STUDIES section*
- Clinical study data (e.g., time to effect) may help inform important dosage information
  - If efficacy of migraine drug significantly decreases after 2 hours, should another dose be administered?

* Section III(C) - Clinical Studies Section of Labeling Guidance

D&A Section #7: What can be Improved?

2 DOSAGE AND ADMINISTRATION

2.1 General

The recommended DRUGOXIDE dosage is 10 mg twice daily. Dosage interruption is recommended for the management of neutropenia *[see Dosage and Administration (2.3)]*. The DRUGOXIDE dosage should be reduced to 10 mg once daily in patients:

- With moderate hepatic impairment
- Receiving strong CYP3A4 inhibitors (e.g., ketoconazole)

2.5 General Considerations for Administration

- DRUGOXIDE should not be used in patients with severe hepatic impairment
- It is recommended that DRUGOXIDE not be initiated in patients with an absolute neutrophil count less than 1000 cells/mm^3.
- Concomitant use of DRUGOXIDE with strong CYP3A4 inducers may result in reduced clinical response to DRUGOXIDE.

2.6 Dosage Modifications

Table 1: Dosage Adjustments for Neutropenia

ANC value (cells/mm^3)	Recommendation
Greater than 1000	No change in dosage
500-1000	Interrupt dosage until ANC is greater than 1000
Less than 500	Discontinue DRUGOXIDE

ANC = absolute neutrophil count

D&A Section #7: Improved Language

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUGOXIDE oral dosage is 10 mg twice daily.

2.2 Dosage Modifications due to Neutropenia

Obtain an absolute neutrophil count (ANC) prior to starting DRUGOXIDE. The use of DRUGOXIDE is not recommended in patients with an ANC less than 1000 cells/mm^3. See Table 1 for recommended dosage adjustments if significant neutropenia occurs during DRUGOXIDE administration.

Table 1: Dosage Adjustments for Neutropenia

ANC value (cells/mm^3)	Recommendation
Greater than 1000	No change in dosage
500-1000	Interrupt dosage until ANC is greater than 1000
Less than 500	Discontinue DRUGOXIDE

2.3 Dosage Modifications with Concomitant Use of Strong CYP3A4 Inhibitors

Reduce the DRUGOXIDE dosage to 10 mg once daily in patients taking concomitant strong CYP3A4 inhibitors *[see Drug Interactions (7.2)]*.

2.4 Dosage Modifications in Patients with Hepatic Impairment

Reduce the DRUGOXIDE dosage to 10 mg once daily in patients with moderate hepatic impairment (DRUGOXIDE is not recommended in patients with severe hepatic impairment) *[see Use in Specific Populations (8.7)]*

D&A Section Example #7: Comments

- Improved organization of D&A section may decrease medication errors
  - D&A section should contain very clear instructions (e.g., subsection titles, titles for tables with text describing information in tables)*
- Should use command language
- Lack of efficacy information with DI belongs in other sections (e.g., DRUG INTERACTIONS)

* Section III(B) - D&A Section Labeling Guidance; DI = drug interactions

D&A Section #8: What can be Improved?

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended DRUGOXIDE dosage is 10 mg once daily.

14 CLINICAL STUDIES
14.1 Clinical Studies in Ulcerative Colitis
Study 1 was a double-blind, placebo-controlled, dosage-ranging 6-week trial in patients with ulcerative colitis. In this trial, patients were randomized to receive placebo, DRUGOXIDE 10 mg once daily, or DRUGOXIDE 10 mg twice daily. Both DRUGOXIDE groups showed improved Mayo scores compared to the placebo group at Week 6 (see Table 5).

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUGOXIDE 10 mg once daily (n=80)	DRUGOXIDE 10 mg twice daily (n=79)
Proportion of Patients with Mayo Score ≤ 2	6%	19%	23%
Proportion of patients with a decrease from baseline in the Mayo score by ≥ 30%	30%	52%	56%

D&A Section #8: Improved Language (Option #1): Two Recommended Dosages

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUGOXIDE dosage is 10 mg once daily or 10 mg twice daily.

In CLINICAL STUDIES section, keep study description and results for both 10 mg once daily and 10 mg twice daily dosages

D&A Section #8: Improved Language (Option #2): Removed Unapproved Dosage from Study Description and Results in Section 14

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUGOXIDE dosage is 10 mg once daily.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a randomized, double-blind, placebo-controlled 6-week trial of DRUGOXIDE in patients with ulcerative colitis. In this trial, patients who received DRUGOXIDE 10 mg once daily showed improved Mayo scores compared to patients who received placebo at Week 6 (see Table 5).

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUGOXIDE 10 mg once daily (n=80)
Proportion of Patients with Mayo Score ≤ 2	6%	19%
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D&A Section #8: Improved Language (Option #3): Removed Unapproved Dosage from Study Results in Section 14

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended DRUGOXIDE dosage is 10 mg once daily.

14 CLINICAL STUDIES

14.1 Clinical Studies in Ulcerative Colitis

Study 1 was a randomized, double-blind, placebo-controlled, 6-week trial in patients with ulcerative colitis. In this trial, patients were randomized to receive placebo, DRUGOXIDE 10 mg once daily, or DRUGOXIDE 10 mg twice daily. DRUGOXIDE 10 mg once daily demonstrated improved Mayo scores compared to the placebo group at Week 6 (see Table 5).

Compared to DRUGOXIDE 10 mg once daily, DRUGOXIDE 10 mg twice a daily did not demonstrate significantly greater reductions in Mayo scores and had a greater incidence of adverse reactions. Therefore, DRUGOXIDE 10 mg twice daily is not recommended *[see Dosage and Administration (2.1)]*.

Table 5: Efficacy Results at Week 6 in Patients with Ulcerative Colitis in Study 1

	Placebo (n=76)	DRUGOXIDE 10 mg once daily (n=80)
Proportion of Patients with Mayo Score ≤ 2	6%	19%
Proportion of patients with a decrease from baseline in the Mayo score by ≥ 30%	30%	52%

D&A Section Example #8: Comments

21 CFR 201.56(a)(3)	"No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness."
21 CFR 201.57(c)(3)(ii)	"Dosing regimens must not be implied or suggested in other sections of the labeling if not included in" the DOSAGE AND ADMINISTRATION section.
21 CFR 201.57(c)(15)(i)	"Any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug … must not imply or suggest … dosing regimens not stated in the … DOSAGE AND ADMINISTRATION section."

D&A Section #9: Complex D&A Instructions - Create a Dosage Overview Subsection: PREPOPIK

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Overview

PREPOPIK, supplied as a powder, must be reconstituted with cold water right before its use *[see Dosage and Administration (2.2)]*. There are two dosing regimens, each requires two separate dosing times:

- The preferred method is the "Split Dose" method and consists of two separate doses: the first dose during the evening before the colonoscopy and the second dose the next day, during the morning prior to the colonoscopy *[see Dosage and Administration (2.3)]*
- The alternative method is the "Day Before" method and consists of two separate doses: the first dose during the afternoon or early evening before the colonoscopy and the second dose 6 hours later during the evening before the colonoscopy) *[see Dosage and Administration (2.4)]*.

Additional fluids must be consumed after every dose in both dosing regimens *[see Dosage and Administration (2.3, 2.4)]*. Instruct patients to consume only clear liquids (no solid food or milk) on the day before the colonoscopy up until 2 hours before the time of the colonoscopy. Instruct patients that if they experience severe bloating, distention, or abdominal pain following the first dose, delay the second dose until their symptoms resolve.

D&A Section Example #9: Comments

Improved organization of D&A section may decrease medication errors

- D&A section should contain very clear instructions (e.g., subsection titles, titles for tables with text describing information in tables)*

* Section III(B) - D&A Section Labeling Guidance

References

- PLR Requirements for Prescribing Information website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

- ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations: http://www.ismp.org/tools/errorproneabbreviations.pdf

Thank you!