

Medical/IDS Review

NDA #: 19-658
Drug Name: Claritin 24 (Loratadine)
Sponsor: Schering-Plough
Subject: CIU Self-Recognition and Label Comprehension Study
Reviewer: Linda Hu, M.D.
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Date: March 26, 2002

This label comprehension study was designed to evaluate Claritin® 24 for over-the-counter (OTC) treatment of chronic idiopathic urticaria (CIU). Claritin® 24 (loratadine) is currently a prescription medication prescribed for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria. Currently CIU is not an OTC indication for any product marketed in the U.S. The label study was designed to evaluate whether consumers can understand label directions, and in particular the new indication and direction for previously diagnosed, recurring or chronic hives. This review did not examine the entire Label Comprehension Study, but focused on issues that will likely be discussed at the Advisory Committee meeting.

The **objectives** of this study were to evaluate if consumers:

- understand the uses, directions and warnings as based on reading the product label
- can accurately self-recognize CIU upon recurrence and appropriately self-select Claritin for use

Study Design

This was an all-comers study enriched with several special populations. Twenty-four marketing research facilities located in twenty-one geographically dispersed markets across the United States were used to complete recruiting and enrollment for this study. Subjects were recruited through advertising, direct mail, and mall intercept for participation. Qualified subjects were asked to read a product label and package insert for Claritin 24 and then were interviewed and asked questions to determine their understanding. Subjects were told that they would be able to refer to the label as needed.

A total of 565 subjects were interviewed for this study. Five study cohorts were defined as follows:

- 1) Cohort 1: Self-recognized CIU sufferers (N=196) who indicate that they have been previously diagnosed by a physician as having the condition;
- 2) Cohort 2: General population (N=116)
- 3) Cohort 3: Low Literacy (N=96)

- 4) Cohort 4: Special cohort who should according to the label “Ask a doctor before use”, such as those who have liver, kidney disease, are pregnant, or are nursing/breast feeding (N=114)
- 5) Cohort 5: Special cohort with a history of hives who did not have a diagnosis of chronic hives or CIU by a physician (N=102); this was the acute hive cohort.

Subjects with CIU (Cohort 1) were recruited by first being asked if they had any of a list of health conditions. If they answered they had hives, they were asked "Has a doctor ever told you that you have recurring or chronic hives with an unknown cause, also known as Chronic Idiopathic Urticaria (CIU)?" If they answered affirmatively, they qualified for Cohort 1. If they answered negatively, they qualified for the acute hive group (Cohort 5).

Key label communication objectives were as follows:

- Claritin relieves and reduces itching and rash due to recurring or chronic hives of an unknown source (CIU)
- Claritin should be used only after being diagnosed by a doctor for recurrent or chronic hives
- The consumer should seek emergency medical attention (if rash, hives, insect bite or sting are accompanied with trouble swallowing, fever above 100° F, wheezing or problems breathing, hives or swelling in or around mouth, drooling, trouble speaking, or joint pain); warnings not to use if allergic to loratadine or other antihistamines; and warnings not to use for hives unless previously diagnosed with CIU by a physician and not to use for food allergies or insect bites and stings.
- This product should not be used to treat food allergies or insect bites or stings

Label Comprehension

Label comprehension was assessed by asking both direct and scenario-based questions. First, the participants were asked directly, as an open-ended question (Q1), what the product was used for, and in addition, another question (Q2) as to whether Claritin was intended for use in any of several listed conditions. Second, a series of scenarios was presented, and participants were asked whether Claritin is intended to be used in the scenario described. For Cohorts 1, 2, 3, and 5, some of the scenarios reflected actual sufferers of CIU. Subjects in Cohort 4 answered a shortened questionnaire to test if they understood that they should ask a doctor before use.

Self-Selection

The label comprehension study questionnaire also included questions relating to “self-selection”. The purpose of this question was to determine if consumers understood whether they *personally* could use Claritin. Because the intent of Cohort 4 was to determine if subjects with liver/kidney/pregnancy/nursing recognized that they should

ask a doctor prior to use, these subjects were asked to assume they had been told by their doctor that they have recurring hives or hives of an unknown source.

As a follow-up to the self-selection question, all cohorts were asked to state reason(s) for their answer. To ascertain whether participants answered correctly regarding self-selection, they were asked a series of medical history/health questions that determined if they had been diagnosed with CIU, had chronic hives, or had contraindications to use.

Self-Recognition

Subjects in Cohort 1 (self-recognized CIU group) were assessed for accurate self-recognition based on a follow-up discussion with a study physician. This assessment was based on a discussion between the subject and the study physician regarding the subject's medical history, and in some cases, subject's selection of a photograph that best represented their skin lesions when they experienced CIU. In other cases, those currently experiencing hives had their hives photographed. In many cases, the photographs of subjects' lesions were of poor quality and were not usable.

Demographics

The demographics of the five study cohorts are summarized in Table 1. An individual participant could be assigned to more than one cohort, so the sum of all cohort totals exceeds the total number of study participants. Two-thirds of the participants were female.

Table 1 Study Populations

Cohort	Male	Female	Total
CIU	49	147	196
General Population	44	72	116
Low Literacy	38	58	96
Contraindicated	47	67	114
Acute Urticaria	35	67	102
Total	193	372	565

The income distribution of the participants in the study cohorts is given in Table 2. The Low Literacy cohort had a significantly higher proportion of subjects in the lowest annual income group, < \$15K. The CIU cohort had a significantly higher proportion of members in the highest income group (>\$75 K annually) than all the other cohorts.

Table 2 Annual Income distribution

	<15K	15K-25K	25K-35K	35K-45K	50K-75K	>75K	Total Responding
CIU	16	22	25	38	45	43	196
General Population	13	20	21	23	19	15	116
Low Literacy	29	20	22	17	3	3	96
Contraindicated	16	19	20	21	19	13	112
Acute Urticaria	12	13	24	25	14	11	102
Total	74	85	101	116	93	76	563

The age distributions of the participants in the study cohorts is given in Table 3. The CIU group had an older population than the general population cohort and the acute urticaria cohort.

Table 3 Age Distribution

	18-34	35-44	45-54	55-64	> 65	Total Responding
CIU	45	47	62	28	14	196
General Population	62	19	18	13	4	116
Low Literacy	32	34	16	10	4	96
Contraindicated	35	22	27	13	17	114
Acute Urticaria	42	23	16	11	10	102
Total	190	132	126	70	47	565

RESULTS

Label Comprehension

Consumer understanding of the product uses was tested by questions 1 and 2 (Q1 and Q2). To be considered “correct”, responders had to state specifically that CIU or recurring/chronic hives, not just hives, was the intended use for the product. Answers were considered “acceptable” if respiratory allergies, hay fever, or allergic rhinitis were mentioned along with CIU since Claritin has been used extensively for this indication. Note, however, that these indications were not listed on the label presented to these consumers in this study. Answers were considered “incorrect” for those who mentioned CIU along with an incorrect product use, such as for colds/flu, other allergic reactions or if just hives in general were mentioned.

Table 4 summarizes the correct and acceptable response rate to these direct questions and several pertinent scenarios relating to product use across the different cohorts.

**Table 4. Product Use – whether consumers understand uses of Claritin
(% Correct/Acceptable)**

Question #	Tab Pg #	Cohorts- % Correct/ Acceptable				
		C1 CIU Suff.	C2 Gen. Pop.	C3 Low Lit.	C4 "Ask Dr. 1st": Liv/Kid/Preg/Nsg	C5 "Do not use" Acute Hives
		a	b	c	d	e
Direct Questions:						
1.) Based on the label, what is this product used for? (open-end)	Pg.14	77 bcde	53	55	58	49
2.) List of conditions that prod. is/is not intended to be used for?	Pg.47	71 bcde	41	48	49	38
Scenarios: Correct and Incorrect Use						
5/6.) Scenario Card B: Use on hives from allergic reaction to peanuts - tongue starting to swell/hard to swallow.	Pg.72	91 be	75	87b	88b	80
7/8.) Scenario Card C: Use on rash from bee sting – trouble breathing.	Pg.85	96 bcde	85	87	88	86
9/10.) Scenario Card D: Diagnosed w/CIU (correct use of product)	Pg.94	99 bcde	96	96	97	95
11/12.) Scenario Card E: Use on red rash due to hiking in woods?	Pg.105	85 be	66	80b	80b	73
15/16.) Scenario Card G: Use on first time break out of hives	Pg.118	90 bcde	73	80	82	75

*The proportions/means are compared for statistically significant differences at the 95% confidence level. A lower case letter next to the percent indicates a value significantly greater than the value in the corresponding column.

Question 1 *Based on the label, what is this product used for? (open-ended question)*

When asked on an open-ended basis what the product was used for, CIU sufferers demonstrated the strongest understanding (77% correct/acceptable). The correct/acceptable response rates for the other cohorts ranged from 49% to 58%. The most common incorrect answer (mentioned by 20% of the total number of subjects) was hives/rash (because the subject did not specify that the hives were chronic). This percentage was 30-40% among the acute hive cohort, depending on how individual responses are classified. It is difficult to elicit specific answers such as chronic hives or hives of an unknown source with an open-ended question. Other common incorrect mentions were “allergies” in general or hay fever. There were also several mentions of asthma, cold/flu, trouble speaking/swallowing, drooling, fever, and joint pain.

Question 2 *Is this product intended to be used for the following conditions? (Ear infections, hay fever, colds, sinus infections, upper respiratory allergies, food allergies, insect bites/stings, a one time breakout of hives, allergies to animal/pets, recurring or chronic hives of an unknown cause)*

CIU sufferers in Cohort 1 scored the highest (71% correct) for this question, with the other cohorts answering correctly in only 38%-49%. However, for to be considered correct for Q2, the subject had to answer correctly for all conditions listed above.

Table 5 lists the number that responded “yes” to this question for each of the previous conditions. In all cohorts combined, 92% of subjects stated this product was intended for use in recurring or chronic hives of an unknown cause, but not all were considered “correct/acceptable” for Q2 because they also stated it is indicated for other incorrect conditions. The highest proportion (71%) gave the correct response, in the CIU cohort.

When the conditions were examined separately, nearly one-quarter (22%) of all participants stated that the product was intended for hay fever, and 18% thought the product could be used for insect bites/stings. Forty-two percent of the general population cohort, 44% of the acute hive cohort, and 20% of the CIU cohort thought that the product could be used for a one time breakout of hives.

For the general population cohort, 39% thought the product was intended for hay fever, 11% for colds, 16% for food allergies, 27% for insect bites/stings, 29% for allergies to animals/pets and 85% for recurring or chronic hives of an unknown cause.

Table 5. (Question 2) Is the product intended to be used for following conditions: (those answering yes)

	Total	CIU	Gen Pop	LL	Preg/Liver /Kidney	Acute Hives
Total Responding	565	196	116	96	114	102
Ear Infections	1.9%	--	1.7%	8.3%	0.9%	2.0%
Hay Fever	21.6%	11.7%	38.8%	22.9%	16.7%	35.3%
Colds	7.6%	0.5%	11.2%	15.6%	4.4%	18.6%
Sinus Infections	9.2%	1.0%	17.2%	13.5%	7.0%	17.6%
Upper Respiratory Allergies	18.1%	8.2%	31.0%	16.7%	13.2%	33.3%
Food Allergies	11.7%	7.1%	16.4%	13.5%	13.2%	20.6%
Insect Bites/Stings	18.4%	9.2%	26.7%	18.8%	23.7%	29.4%
One Time Breakout of Hives	32.0%	19.9%	42.2%	36.5%	37.7%	44.1%
Allergies to Animals/Pets	17.7%	9.7%	29.3%	21.9%	14.0%	31.4%
Recurring or Chronic Hives of an Unknown Cause	91.7%	99.0%	85.3%	84.4%	89.5%	92.2%

A series of scenarios was also presented to study participants. These questions and the percent correct in each cohort is also summarized in Table 4. The scenarios from this table are provided in their entirety as follows.

Scenario B “Jane is allergic to peanuts, and she accidentally ate a candy bar that had peanuts in it. Her arms have broken out into hives. Her tongue has started to swell and it is getting hard for her to swallow. She wants to take something to help her.”

“Based on the label, is this product intended to be used for this situation, or not?”

Scenario C “Pam was working in the garden and got stung by a bee. She suddenly developed a rash and is having trouble breathing.”

“Based on the label, is this product intended to be used for this situation, or not?”

Scenario D “For the past several months, Ted has broken out in hives about every week. His doctor told him he has a condition called “Chronic Idiopathic Urticaria” or recurrent hives of an unknown source or no known cause.”

“Based on the label, is this product intended to be used for this situation, or not?”

Scenario E “Bill is on a hiking trip through the woods and developed an itchy red rash on his legs. He wants to take something to relieve his symptoms”

“Based on the label, is this product intended to be used for this situation, or not?”

Scenario G “Sue broke out in hives on her arms and legs for the first time in her life. She would like to take a product to treat the hives.”

“Based on the label, is this product intended to be used for this situation, or not?”

Self-Selection

Questions (Q17/18) *Considering everything on the package label, is this product intended for you, personally, to take home and start using? Why do you say that?*

The purpose of the "self-selection" series of questions was to determine if consumers understood whether they *personally* could use Claritin based on their personal history of hives, as well as their current medications and medical conditions. Using this information, the Sponsor classified subjects as belonging to one of three categories: “OK to use”, “Ask a doctor first”, and “Do not use”.

For the self-selection question, a high proportion of previously diagnosed CIU sufferers (Cohort 1) gave correct or acceptable answers (Table 6). However, a significant proportion of those in the general population (Cohort 2) and acute hive population (Cohort 5), 30% and 46% respectively, gave incorrect responses.

Table 6. Self-Selection Question (Q17/18)

SELF-SELECTION: Whether consumers understand if they can personally use Claritin® .							
Objective	Question #	Tab Pg #	Cohorts- % Correct/ Acceptable				
			C1 CIU Suff. (OK to use)	C2 Gen. Pop. (Do not use)	C3 Low Lit. (Do not use)	C4 “Ask Dr. 1st”: Liv/Kid/ Preg/Nsg	C5 “Do not use” Acute Hives
Whether consumers understand if they can personally use Claritin® .	17/18/19/20.) Considering everything on the package label, is this product intended for you, personally, to take home and start using?	Pg.152	100	70	65	80	54

In the general population (Cohort 2), the large majority of whose members should not use, there were 73 correct or acceptable answers from 104 responding (70%) in the group. Of those in Cohort 2 who should ask a doctor first, 7/8 (87%) answered correctly or acceptably, while all of those who evaluated as OK to use did self-select to use, 4/4 (100%). The fraction of general population participants who decided correctly not to use is marginal. Of those who answered incorrectly, 19% stated the product was intended for allergic rhinitis or allergies, 19% stated it relieved itching/rash, 16% stated it relieved hives, and 9% said it relieved chronic/recurrent hives.

In the acute urticaria group (cohort 5) who should not use or should ask a doctor, 55/102 (54%) gave correct or acceptable answers. They stated that the product was not intended for their use or that they would “ask their doctor” prior to use. This is a low percentage of correct answers. Of those who answered incorrectly, at least 23% stated that the product could be used to relieve hives, 21% stated the drug relieves chronic/recurring hives, 15% stated relieves itching/rash, and 11% responded that the product can be taken for allergies or allergic rhinitis. The respondents that answered the product is intended to treat chronic/recurring hives did not have a physician diagnosis of CIU (although this is not explicitly stated in the submission).

The results of this question indicate that 46% of consumers with acute urticaria will incorrectly decide to self-treat with Claritin. Of consumers in the general population who should not use, about 30% will self-select to use the drug.

Self-Recognition

Only subjects in Cohort 1, CIU Sufferers (self-reported), participated in this arm of the study. In order for the subjects to be evaluated on the ability to self-recognize chronic idiopathic urticaria, they spoke with a nurse and a study physician at West™s Central Medical Operations Group (CMOG). Nearly all of the subjects (94%) who self-reported having CIU were confirmed by the physician as having CIU.

DISCUSSION

The study results suggest that over 90% of consumers with a previous diagnosis of CIU, about 30% of consumers from the general population without a previous diagnosis, and about 46% of those with acute hives believe that the product is intended for their use. Incorrect reasons for self-selecting to use the drug included: the product was to be used for hives without specifying chronic, acute hives, allergic rhinitis, itching/rash, or chronic/recurrent hives without a prior physician diagnosis. There were also several mentions of asthma, cold/flu, trouble speaking/swallowing, drooling, fever, and joint pain. Question 2 showed that in the general population cohort, 39% thought the product was intended for hay fever, 11% for colds, 16% for food allergies, 27% for insect bites/stings, 42% for a one time break out of hives, 29% for allergies to animals/pets.

The study suggests that some consumers who do not have a prior diagnosis of CIU will not make the distinction between general hives, acute hives, and chronic urticaria when deciding whether this product may be right for them to use. Others will use for generally accepted indications for Claritin. An important issue is whether consumers with symptoms of anaphylaxis recognize that they should seek immediate medical attention. Although study participants were shown scenarios describing anaphylaxis, they were not asked specifically whether or when to seek medical attention.

* The Agency has asked the Sponsor to further categorize, summarize and quantify responses to some questions since results were primarily presented as raw data