

Medical Review

NDA #: 19-658/S-018

Drug Name: Claritin (loratadine)

Sponsor: Schering Corporation

Reviewer: Charles J. Ganley, M.D.

Correspondence Date: January 25, 2002

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In support of their supplemental NDA for the switch of the Chronic Idiopathic Urticaria (CIU) indication for Claritin from prescription to OTC, the sponsor has submitted a consumer survey, a physician survey, an expert panel report and a labeling comprehension study. This review summarizes the results of the consumer and physician surveys and comments on the Expert Panel report. The labeling comprehension study is reviewed in a separate FDA document.

Consumer Survey

Design

The consumer survey was conducted through the National Family Opinion Interactive Panel. This is a website-based group that allows any Internet user to register for their survey participant list. Registered users are informed of survey opportunities via e-mail and can decide in which surveys they choose to participate. Participation in a survey allows users to accumulate points that can be used for prizes or cash.¹ In this case, an e-mail was sent to over 500,000 households each for two consecutive weeks in October-November 2001. A screening survey was used to help identify a chronic urticaria population by asking, "Have you ever been diagnosed by a medical doctor as having chronic or recurrent hives that have no known discernable cause (also known as chronic urticaria)." Each e-mail mailing yielded approximately 15,000 qualified adult subjects (older than 18 years of age).

A more detailed interactive survey was conducted in 845 subjects randomly sampled from the pool of subjects. The sample size was chosen so that 300 chronic idiopathic urticaria sufferers would complete the survey. This would allow for an error of +/- 6% at a 95% confidence interval. Questions in the survey were either open ended or multiple choice.

The objectives of the survey were as follows:

- To obtain information on the frequency and severity of symptoms from a patient perspective;
- To obtain information on the patient interaction with their physician;
- To obtain information on treatment modalities;
- To obtain information on a patient's perspective on the ability of patients to recognize symptoms and determine what actions should be taken during an attack.

Results

Of the 845 subjects, 388 subjects completed the survey². The average age was 45 years, 66% were female and 84% were white. The majority of subjects had experienced recurring hives for greater than 3 years (68%). Thirteen percent had the condition for less than one year. Most were diagnosed with chronic hives more than three years prior to the survey (59%). Approximately 39% had episodes "all of the time" or at least every month. A majority of subjects had four or more episodes each year (58%). The episodes resolve within a week for 66%. Approximately 51% experienced an episode in the past month.

Itching (81%), hives or wheals (77%) and redness (68%) were the most common symptoms. Itching (56%) and hives (25%) were listed as the most prominent symptoms during an attack. Individuals were more likely to have hives in multiple areas simultaneously (62% had 8 or more hives at one time). Most did not view the condition as serious (73%). During an attack, most use a prescription or OTC medication.

¹ 1000 points is equivalent to approximately \$10. Up to 1500 points can be obtained for taking a survey.

² 457 subjects did not complete the survey for the following reasons: 192 did not respond, 95 logged on after the survey closed, 81 did not suffer from CIU on requalification, 81 worked in sensitive occupations (e.g. advertising, pharmaceuticals), 1 was not > 18 years old, 7 did not want to take the survey

Approximately 20% of the subjects contact their physician when they have an attack (78 of 388). Only 21% of these subjects contacted the physician immediately and an additional 33% waited a day or less before contacting the physician.

Most subjects (94%) felt it was easy to identify the condition when it appeared. Prior to seeing a physician, over 90% used an OTC medication to treat the condition. The majority of these subjects used an OTC antihistamine (62%). There was no consensus for the name given the condition by the physician at the initial visit. Chronic idiopathic urticaria was used less than 10% of the time.

When asked what they would do if they developed difficulty breathing, fever or trouble swallowing during an attack, 95% would go to the emergency room or visit their doctor. Only 5% would use the medicine already prescribed. This was a multiple-choice question. An open-ended question in this instance would be more appropriate to decrease the chance of biasing the respondent.

Discussion

It is difficult to interpret these surveys for the following reasons:

- It is difficult to validate whether the subjects who participated actually have the underlying condition;
- Because many of the questions are multiple choice and not open-ended, this limits the range of answers that would have been provided by the respondents and may influence the respondents answer;
- The results of this survey are not reproduced in another cohort of subjects with chronic urticaria; and
- It assumes that the population who participated are representative of the overall population of chronic urticaria sufferers.

If it is assumed that the majority of subjects have the underlying condition, then there are some interesting observations.

- It is not surprising that the majority of subjects, after the initial diagnosis by a physician, would self-identify the condition and not call the doctor. They were given either prescription medication or instructed to use OTC medication by the physician for the next attack.
- It is not surprising that many attempted to treat the symptoms with an OTC topical product indicated for itching prior to seeing a physician. Itching was the most common symptom (in 81%) and the most prominent (in 56%) in this group of respondents. What is surprising is that 62% used OTC anti-histamines prior to seeing a physician. OTC anti-histamines are not indicated for this condition or for the symptoms associated with a rash. It is unclear whether they sought the advice of another health provider, pharmacist or used alternative resources (e.g. the Internet) in deciding to use an anti-histamine before seeking the opinion of a physician.
- The screening question for continuing in the survey used the descriptor “chronic or recurrent hives that have no known/discernable cause (also known as chronic urticaria).” The responses to subsequent questions on how the physician described the condition at the initial visit (page 25 of the report) may have been influenced by this screening question. In any event, there was no consensus descriptor for this condition. Chronic Idiopathic Urticaria was used infrequently. The most common descriptors included the word hives. Clearly, the most important descriptor on any label would have to include the word hives. It is unclear what other defining terms should be included.
- The answers to the question regarding what the consumer would do if they experienced symptoms such as difficulty breathing, fever or trouble swallowing is difficult to interpret because multiple choices were given. It is not clear how they would have responded had it been an open-ended question. Aside from the answer regarding a visit to the emergency room, the sense of urgency is not discernable. For those who responded that they would call or visit a physician, the timing of this call or visit was not elicited.

Physician Survey

The physician survey used Internet based databases as their source of respondents³. The survey was conducted between November 13, 2001 to November 15, 2001 by Marketing Measures, Inc. Physicians were pre-screened for their specialty and whether they treated patients with CIU. The survey

³ databases: Medical Marketing Conference, Medscape or ePocrates

included 359 qualified Internet interviews from physicians with backgrounds in Primary Care (151), Dermatology (75), Allergy (55) and Pediatrics (78)⁴.

The survey collected information on the practice patterns of these physicians regarding the diagnosis and treatment of patients with hives. The deficiencies of the survey are similar to those described in the consumer use study. The information is anecdotal and is generally not helpful in assessing the use of loratadine in the OTC setting.

Expert Panel Report

The sponsor organized a panel of expert consultants to address two questions:

- 1) Can a patient self-recognize and safely self-treat a recurring episode of chronic idiopathic urticaria with OTC loratadine after initial diagnosis by a physician?
- 2) Are there serious medical consequences from a patient self-treating hives with OTC loratadine without prior consultation with a physician? If so, can these consequences be mitigated with labeling?

Based on personal experience, the panel believed that patients diagnosed with chronic idiopathic urticaria could self treat their condition because most already do it after the initial diagnosis by a physician. Although they provided no data to support this position, it certainly is not unrealistic if one can be assured that the patient would get the diagnosis in the first place.

The panel also felt that this population was not at greater risk than the general population for more serious conditions (e.g. anaphylaxis). Despite this, they recommend labeling instructing subjects to seek immediate medical help for symptoms such as “difficulty breathing, faintness, swelling of the tongue or in the throat, or gastrointestinal distress”. This is somewhat contradictory unless the purpose is to reinforce what is already told to them by a physician at the time of diagnosis.

They also recommend that the indication be limited to the CIU population because 1) patients with recurring hives should have an evaluation by a physician; and 2) “data are not now available for a broader urticaria indication”. This position and recommendation are perplexing in view of the information available from the consumer survey of patients with “chronic urticaria” and the label comprehension study. Presumably, the sponsor made this information available to them. If the consumer survey is to be believed, consumers are already using OTC anti-histamines for the treatment of hives and physicians are not adequately evaluating them for other conditions⁵. The broader use of anti-histamines for hives already appears to be prevalent in the general population based on the consumer survey. It would be very difficult to reverse that practice if it is accurate.

One of the major deficiencies of the report is that it fails to address the issue of accurate self-selection in the general population. Although this was not one of the questions they were asked to answer, it should have come up in the course of discussion. Because of the failure to address the accuracy of self-selection, there is an underlying assumption that whatever is written on a package will be adhered to by consumers. The data in the sponsor’s database do not support this.

Summary

The sponsor notes that "urticaria is a rather common condition with an estimated incidence of 10 - 20 percent of the U.S. population". "About one-fifth of the urticaria cases are chronic- - persisting more than six weeks and the vast majority of chronic sufferers have an idiopathic disorder." Based on this information, the majority of consumers who experience urticaria will not have chronic hives. One of the important issues to be addressed for this indication is accurate self-selection, de-selection and use by all consumers likely to use this product. The consumer survey and physician surveys do not provide sufficient information on the ability of consumers to accurately select and use this product.

The Expert Panel Report is also deficient in providing supporting information for the accurate self-selection and use of the product. There appears to be an underlying assumption in their recommendation that simply writing instructions on the label limiting use to the CIU population will lead to consumer compliance. Contrary to the recommendation of the panel, the Agency should also consider a more general hives indication in the general population and determine what information should be provided to support this claim.

⁴ "Qualified " interview was not defined

⁵ In the consumer survey, 7% had skin testing and 39% had blood testing.

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