DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: May 8, 2001

3764 '01 MAY 10 P3:13

From: Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification for New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient:	N-Acetyl-L-Hydroxyproline
Firm:	Kyowa Hakko U.S.A., Inc.
Date Received by FDA:	February 9, 2001
90-Day Date:	May 10, 2001

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on pubic display in docket number 95S-0316 **after** May 10, 2001.

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 93

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC

3765 '01 MAY 10 P3:13

APR 24 2001

Neil C. Sullivan
Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, New York 10022

Dear Mr. Sullivan:

This is in response to your letter and addendum, respectively dated January 5, 2001 and February 7, 2001, making a submission for a new dietary ingredient pursuant to 21 U.S.C. § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)). Your letter notified FDA of your intent to market the substance "N-Acetyl-L-Hydroxyproline (AHYP)" as a new dietary ingredient.

You state in your submission that AHYP is "an ideal candidate for a new dietary supplement that acts on the treatment of arthritis." Under 21 U.S.C. § 321(g)(1)(B), a drug is defined as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease. The information in your submission represents that a product containing AHYP is intended to be used to treat arthritis and therefore, is subject to regulation as a drug under 21 U.S.C. § 321(g)(1)(B) and not as a dietary supplement. See 21 CFR § 101.93(g). If you wish AHYP to be evaluated for its use in the treatment of arthritis, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

21 U.S.C. § 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C § 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. § 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

As we have stated above, your product containing AHYP is subject to regulation as a drug. Nonetheless, we have carefully considered the information in your submission concerning whether a dietary supplement containing AHYP will reasonably be expected to be safe if it

were able to be marketed as a dietary supplement. We have significant concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing AHYP will reasonably be expected to be safe. Your submission indicates that use of AHYP may result in adverse effects. You state that adverse effects include, among other things, gastrointestinal complaints (e.g., nausea and diarrhea), allergic reactions, arthralgia, vasculitis urticaria, and allergic eosinophilia. In a search of the scientific literature, we found a clinical trial that reported that 25 out of 132 (18%) arthritic patients treated with 1200 mg/day AHYP (a dose within your recommended intake) experienced adverse effects, with eight patients withdrawing from the study as a result of these effects.[1] The reported effects included gastrointestinal pain, nausea, vomiting, constipation, palpitations, dizziness, and skin rash. Although you recognize that potentially serious side effects are expected to occur with the use of AHYP, your submission contains no explanation or data that explain why these potentially serious side effects are not grounds for concluding that AHYP is not safe. Further, the scientific studies you cite do not provide an adequate basis for a conclusion that the dietary supplement will reasonably be expected to be safe. The studies you submitted were not designed nor intended to examine the adverse or toxicological effects of AHYP in healthy people; rather, the studies mostly appear to be designed to evaluate its short-term effect in persons suffering from serious diseases. Such efficacy studies have limited utility for determining whether the long-term use of a substance as an ingredient in dietary supplements is safe for healthy people.

AHYP is an anti-inflammatory agent, displaying antiphlogistic and analgesic pharmacological properties. However, your submission does not address the potential serious risks that might exist for persons already taking drugs or other products with similar pharmacological effects, if any, that would result from the use of products containing AHYP at your recommended intake.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that AHYP, when used under the recommended or suggested conditions of use in the labeling of a dietary supplement, will reasonably be expected to be safe. Because the information in your submission indicates that your product is a drug and not a dietary supplement, not only would your product be subject to regulation as a drug if marketed, but, even insofar as it might be argued that your product is a dietary supplement, a dietary supplement containing AHYP would be deemed adulterated and subject to regulatory action pursuant to 21 U.S.C. 342(f)(1)(B) (section 402(f)(1)(B) of the Act). Further, introduction of a product containing AHYP into interstate commerce is prohibited under 21 U.S.C. § 331(v). Therefore, a dietary supplement containing AHYP would be deemed

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[1] Herrmann G; Steeger D; Klasser M; Wirbitzky J; Furst M; Venbrocks R; Rohde H, Jungmichel D; Hildebrandt HD; Parnham MJ; Gimbel W; Dirschedl H (2000). Oxaceprol is a well-tolerated therapy for osteoarthritis with efficacy equivalent to diclofenac. *Clin Rheumatol.* 19:99-104.

adulterated and subject to regulatory action pursuant to 21 U.S.C. § 331(v). In any event, you are not prohibited from submitting a new premarket notification for AHYP under 21 U.S.C. 350b(a)(2), if you deem such resubmission appropriate.

Should you have any questions concerning this matter, please contact us at (202) 205-4168.

Sincerely yours,

Felicia B. Satchell

Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

MAR 26 2001

3766 '01 MAY 10 P3:13

Mr. Neil Sullivan
Manager
Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, New York 10022

Dear Mr. Sullivan:

This is to inform you that the notification and addendum, respectively dated January 5, 2001 and February 7, 2001, you submitted pursuant to 21 U.S.C. 350b(a)(2) were filed by the Food and Drug Administration (FDA) on February 9, 2001. Your notification concerns the substance called "N-Acetyl-L-Hydroxyproline (AHYP)" that you assert is a new dietary ingredient.

In accordance with 21 C.F.R § 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date (i.e., after April 25, 2001), you must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains "N-Acetyl-L-Hydroxyproline (AHYP)."

Please note that acceptance of this notification for filing is a procedural matter and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. As another procedural matter, your notification will be kept confidential for 90 days after the filing date. After May 10, 2001, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any information that is trade secret or otherwise confidential commercial information in the notification will not be disclosed to the public.

Please contact us at (202) 205-4168, if you have any questions concerning this matter.

Sincerely yours,

Rhonda R. Kane, M.S., R.D.
Consumer Safety Officer
Dietary Supplements Team
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, NY 10022

Telephone: 212 319-5353
Facsimile: 212 421-1283

KYOWA

February 7, 2001

Office of Special Nutritionals
HFS-800-820
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

RE: **Amended Submission**
of New Dietary Ingredient Notification
for N-Acetyl-L-Hydroxyproline

To whom it may concern:

1. As per my recent telephone conversation with Peggy Carlson, Head of Dietary Supplement Team we are instructed to omit the references that need an English translation. Therefore, please **omit** the following numbered references:

References No.'s **1, 2, 4, 5, 6, 27** concerning the mechanisms of action of AHYP
Reference No. **10** concerning the effect of AHYP on burn tissue
Reference No. **11** concerning the effect of AHYP on nicotine toxicity
Reference No. **16** concerning different subject
Reference No. **17** general notes on OA treatment
Reference No. **18** A small scale clinical study
Reference No.'s **19, 20, 21, 22** Human OA clinical trials of Oxaceprol (non-English with a summary in English)
Reference No.'s **23, 28** A brief review of the efficacy of Oxaceprol in humans
Reference No. **26** RA clinical study
Reference No.'s **31, 33, 35** Dermatological use of AHYP in humans
References No. **34**, AHYP is not mentioned
Reference No.'s **32, 36,37** AHYP on ulcer, nicotine, cicatrization, respectively

2. For your further knowledge about AHYP, here enclosed is a product description by the German pharmaceutical company Chephasaar. The product is trade named *AHP 200 Oxaceprol*. The original German product information or fact sheet is attached with the English translation. The fact sheet is informative because it describes the toxicological properties and the efficacy of AHYP.

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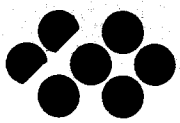

Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration

RE: **Amended Submission**

3. For your convenience we summarize here below the remaining English written references of our original submission:

Reference No. **3**, mechanisms of action
Reference No. **7**, patents
Reference No. **8**, mechanisms of action
Reference No. **9**, pharmacokinetics in dogs for reference of safety data
Reference No.'s **12**, **13**, **14**, effectiveness in rat and mouse inflammation
Reference No. **15**, effectiveness in rabbit OA model
Reference No. **24**, abstract details long term clinical data of Oxaceprol
Reference No. **25**, abstract details effectiveness and tolerability of Oxaceprol
Reference No. **29**, review on Oxaceprol with comments on dosage and safety in humans
Reference No. **30**, review on anti-OA drugs

In closing we trust this modification will allow you to proceed with the review and consideration of the data we have presented for the submission.

In the event you need to contact Kyowa Hakko, please contact the undersigned.

Sincerely,

Neil Sullivan
Manager
Kyowa Hakko USA

enclosures

AHP 200®

Wirkstoff: Oxaceprol

1. **Bezeichnung des Arzneimittels**
AHP 200®
Wirkstoff: Oxaceprol

2. **Verschreibungsstatus/Apothekenpflicht**
Verschreibungspflichtig

3. **Zusammensetzung des Arzneimittels**

a) Stoff- oder Indikationsgruppe
Antirheumatikum

b) Zusammensetzung

arzneilich wirksame Bestandteile
Eine Filmtablette enthält
200 mg Oxaceprol.

Sonstige Bestandteile
Talkum, Magnesiumstearat, Kartoffelstärke, Makrogole, Polymethacrylat, Povidon, Propylenglykol, Simethicon, Farbstoffe E 171, E 104, E 110.

4. **Anwendungsgebiete**
Degenerative Gelenkerkrankungen in schmerzhaften oder entzündlichen Stadien (Arthrosen z.B. des Knies, der Hüfte, der Schulter, der Wirbelsäule, der kleinen Gelenke; Polyarthrosen; Chondropathia patellae), Arthritis, Periarthritis, Bursitis, Tendinitis, Tendovaginitis.

Entzündliche Bindegewebserkrankungen.

5. **Gegenanzeigen**
Bekannte Überempfindlichkeit gegenüber Oxaceprol oder einem der sonstigen Bestandteile.

Obwohl es bisher keinen Hinweis auf etwaige teratogene Wirkungen von Oxaceprol gibt, sollte auf die Anwendung von AHP 200® während einer Schwangerschaft verzichtet werden.

6. **Nebenwirkungen**
Unter der Behandlung mit Oxaceprol werden gelegentlich beobachtet: gastrointestinale Beschwerden wie Übelkeit, Appetitstörung, Magenschmerzen oder Diarrhöe, die häufig passagerer Natur sind. Selten kommt es zu allergischen Reaktionen (Hautrötung, Hautjucken, Exantheme). In Einzelfällen wurden folgende Reaktionen allergischer Genese beschrieben: Haarausfall, Gelenkschmerzen, Vaskulitis, Urtikaria, Quincke-Ödem, allergische Eosinophilie.

7. **Wechselwirkungen mit anderen Mitteln**
Bei Patienten unter antikoagulativer Therapie mit Vitamin-K-Antagonisten (z. B. Marcumar®) kann eine Beeinflussung der Blutgerinnung durch Oxaceprol nicht ausgeschlossen werden. Eine engmaschige Kontrolle der Prothrombinzeit unter der gleichzeitigen Therapie mit AHP 200® wird daher empfohlen.

8. **Warnhinweise**
entfällt

9. **Wichtigste Inkompatibilitäten**
bisher nicht bekannt

10. **Dosierung**
Soweit nicht anders verordnet, beträgt die Normdosierung 3 x täglich 1 Filmtablette. Je nach Schwere der Erkrankung kann die Tagesdosis, besonders zu Beginn einer Behandlung, auf 3 x 2 Filmtabletten erhöht werden.

11. **Art und Dauer der Anwendung**
AHP 200® Filmtabletten werden vorzugsweise vor einer Mahlzeit unzerkaut mit ausreichend Flüssigkeit eingenommen.

Die Dauer der Einnahme ist von der Art und der Ausprägung der Erkrankung abhängig und ist individuell festzulegen.

12. **Notfallmaßnahmen, Symptome und Gegenmittel**
Intoxikationen beim Menschen sind bisher nicht vorgekommen und auch nur schwer vorstellbar. Bei oraler Verabreichung im Tierversuch wurden erst ab dem 500- bis 1000fachen der im Humanbereich üblichen Normdosierung von 10 mg/kg Körpergewicht toxische Effekte beobachtet (Sedierung, Ptosis, Piloarrektion).

13. **Pharmakologische und toxikologische Eigenschaften, Pharmakokinetik**

a) Pharmakologische Eigenschaften
Oxaceprol zeigt eine ausgeprägt antiphlogistische und analgetische Wirksamkeit.

In präklinischen Studien ist die antiphlogistische Effektivität in verschiedenen Modellen (Carrageenin-Pfotenödem, anaphylaktischer Gelenktest, Carrageenininduzierte Pleuritis, Adjuvans-Arthritis) und im Vergleich zu Referenzantiphlogistika (Indometacin, ASS, Phenylbutazon, Ibuprofen) mit ausgezeichnetem Ergebnis geprüft worden. Diese Daten sind anhand eines Pyrexal-Erythems auch im Humanmodell bestätigt.

Die analgetische Wirksamkeit ist durch den Randall-Selitto- und den Phenylchinon-Writhing-Test gezeigt worden.

Klinisch ist Oxaceprol in verschiedenen Indikationsgebieten degenerativer Gelenkerkrankungen geprüft worden. In Placebokontrollierten Studien sowie in doppelblind und randomisiert durchgeführten Studien gegen Ibuprofen und Diclofenac ist die Substanz in der Therapie von Gon-, Cox- und Spondylarthrosen eingesetzt worden. Während der Cross-over-Test versus Placebo die signifikante Überlegenheit von Oxaceprol zeigte, ist die Wirksamkeit der Substanz derjenigen von Ibuprofen und Diclofenac hinsichtlich der symptomatischen Effektivität ebenbürtig.

In der Therapie der Rheumatoiden Arthritis zeigt Oxaceprol eine tendenzielle Überlegenheit zu Diclofenac.

In allen Indikationsgebieten werden die typischen Schmerzparameter (z.B. Anlauf-, Ruhe- und Belastungsschmerz), aber auch Entzündungs- und Beweglichkeitsparameter deutlich gebessert.

b) Toxikologische Eigenschaften

akute Toxizität

Bei oraler Gabe beträgt die LD50 bei der Ratte 7.451 mg/kg KG, bei der Maus 5.688 mg/kg KG; bei i.m. Applikation bei Ratte bzw. Maus mehr als 4.000 mg/kg KG bzw. 2.921 mg/kg KG.

chronische Toxizität

Die Toxizität nach wiederholter Verabreichung wurde an Ratten und Beagles bestimmt. Dazu erhielten die Tiere an 29 bzw. 28 aufeinanderfolgenden Tagen 3 Dosierungen des Wirkstoffs (4,5; 36; 288 mg/kg KG). Bei den Ratten traten auch in der höchsten Dosierung bis auf lokale Effekte durch die Applikation (entzündliche Prozesse an der Injektionsstelle) keine unerwünschten Wirkungen auf. Beim Hund traten bei den zwei niedrigeren Dosierungen keine Effekte auf. In der höchsten Dosierung wurden leichte Veränderungen an Cornea und Nierentubuli beobachtet, deren pathologische Bedeutung nicht bekannt ist. Todesfälle traten nicht auf.

Mutagenität

Oxaceprol wurde umfassend auf mutagene Eigenschaften überprüft. Es ergaben sich keine Hinweise auf mutagenes Potential.

Cancerogenität

Untersuchungen zur Cancerogenität liegen nicht vor; aus Tierversuchen und klinischen Untersuchungen ergeben sich keine Hinweise auf tumorigenes Potential.

Reproduktion

Im Kaninchen wurden bei der höchsten Dosierung von 288 mg/kg/d teratogene Effekte beobachtet, die sich in einer zweiten, identisch angelegten Studie jedoch nicht reproduzieren ließen. Daten zum placentaren Transport von Oxaceprol beim Menschen sowie Daten zum Übertritt in die Muttermilch liegen nicht vor.

c) Pharmakokinetische Eigenschaften

Resorption

3,5 Stunden nach oraler Applikation von Oxaceprol liegen maximale Plasmaspiegel vor. Die Bioverfügbarkeit nach oraler Gabe beträgt etwa 30%.

Verteilung

Auf Grund seiner Wasserlöslichkeit verteilt sich Oxaceprol im gesamten Organismus. Es geht in die Synovialflüssigkeit über. Plasma-Eiweißbindung ist nicht nachgewiesen. Es gibt keine Hinweise auf Kumulation.

Elimination

Nach i.m. oder i.v. Applikation beträgt die Eliminationshalbwertszeit durchschnittlich 2 Stunden. Die Elimination erfolgt ausschließlich renal. Die Ausscheidung erfolgt unverändert und vollständig. Oxaceprol wird weder inkorporiert noch metabolisiert.

14. Sonstige Hinweise

entfällt

15. Haltbarkeitshinweise

AHP 200® Filmtabletten sind 3 Jahre haltbar. Nach Ablauf des Verfalldatums soll das Arzneimittel nicht mehr angewandt werden.

16. Lager- und Aufbewahrungshinweise

keine

a) Entsorgungshinweis

Unverbrauchte Reste des Arzneimittels müssen keiner gesonderten Entsorgung zugeführt werden.

17. Darreichungsform und Packungsgrößen

100 Filmtabletten (N3)
300 Filmtabletten

18. Stand der Information

März 1999

19. Name oder Firma und Anschrift des pharmazeutischen Unternehmers

Hersteller/pharm. Unternehmer:
Chephasaar
Chem.-pharm. Fabrik GmbH
Mühlstraße 50
66386 St. Ingbert
Telefon: (0 68 94) 971 - 0
Telefax: (0 68 94) 971 - 199

Mitvertrieb:
Rosen Pharma GmbH
66377 St. Ingbert

Vertrieb:
MIP Pharma GmbH
66386 St. Ingbert

1. **Name of the drug**
AHP 200®
active agent: Oxaceprol

2. **Prescription status**
Ethical drug

3. **Composition of the drug**

a) Group of substances or indications
Antirheumatic agent

b) Composition

Medically effective components
One film-coated tablet contains
200 mg of Oxaceprol.

Other components
Talcum, magnesium stearate, potato starch, Makrogole, polymethacrylate, Povidon, propylene glycol, Simethicon, colours E 171, E 104, E 110.

4. **Fields of application**
Degenerative joint diseases in painful or inflammatory phases, arthroses e. g. of the knee, the hip, the shoulder, the spinal column, the small joints; polyarthroses; chondropathy patellae, arthritis, periarthritis, bursitis, tendinitis, tendovaginitis.

Inflammatory connective tissue diseases.

5. **Contra-indications**
A known hypersensitivity to Oxaceprol or one of the other components.

Although up to now there are no indications that Oxaceprol may have possible teratogenic effects, it is recommended not to use AHP 200® during a pregnancy.

6. **Side effects**
Under the treatment with Oxaceprol occasionally there have been observed: gastrointestinal complaints, such as nausea, impaired appetite, pain in the stomach or diarrhea, which are often of a passing nature. Seldom there may occur allergic reactions (a reddening of the skin, an itching of the skin, exanthemae). In exceptional cases the following reactions of allergic genesis were described: loss of hair, arthralgia, vasculitis, urticaria, giant urticaria, allergic eosinophilia

7. **Interactions with other agents**
In patients under anticoagulative therapy with vitamin K-antagonists (e.g. Marcumar®) an affection of coagulation by Oxaceprol cannot be excluded. A closemeshed control of the prothrombin time under simultaneous therapy with APH 200® is, therefore, recommended.

8. **Warning notices**
Doesn't apply.

9. **Most important incompatibilities**
Not known up to now.

10. **Dosage**
As far as not differently prescribed, the standard dosage is 3 x daily 1 film-coated tablet. Depending on the severity of the affection, specially at the beginning of the treatment the daily dose can be increased to 3 x 2 film-coated tablets.

11. **Method and period of application**
AHP200® film-coated tablets are preferably taken before a meal, unchewed, with sufficient liquid.

The period of time for which the drug is to be administered depends on the character and intensity of the affection and is to be fixed individually.

12. **Emergency procedures, symptoms and antidotes**
Intoxications in humans have not occurred up to now and are actually hardly imaginable. In oral administration during bio-assays, only above the 500- to 1000-fold quantity of the standard dosage usual in the human field (10 mg/kg of body weight) toxical effects could be observed (sedation, ptosis, piloerection).

12. **Pharmacological and toxicological properties, pharmacokinetics**

a) Pharmacological properties
Oxaceprol shows a distinct antiphlogistic and analgesic efficacy.

In preclinical studies the antiphlogistic efficacy has been tested with an excellent result in various models (carrageenine paw edema, anaphylactic joint test, carrageenine-induced pleurisy, adjuvant-arthritis) and in comparison to reference antiphlogistics (indometacin, ASA, phenylbutazone, ibuprofen). These data have also been confirmed with a pyrexal erythema in the human model.

The analgesic efficacy has been shown by the Randall-Selitto and the Phenylchinone-Writhing-test.

Clinically Oxaceprol has been tested in various indication fields of degenerative joint diseases. In placebo-controlled studies as well as

double-blind and randomised studies against ibuprofen and diclofenac the substance has been applied in the therapy of gon-, cox- and spondyl-arthrosis. While the cross-over test versus placebo showed the significant superiority of Oxaceprol, the substance is equal to ibuprofen and diclofenac in its symptomatic efficacy.

In the therapy of rheumatoid arthritis Oxaceprol shows a tendency of superiority to diclofenac.

In all indication fields the typical pain parameters (e.g. pain when starting to move, rest pain and pain following exercise), but also inflammation and flexibility parameters were distinctly improved.

b) Toxicological properties

Acute toxicity

When orally administered, the LD_{50} in rats is 7.451 mg/kg of body weight, in mice 5.688 mg/kg of body weight; when IM-applied in rats and mice, respectively, it was more than 4,000 mg/kg and 2,921 mg/kg of body weight, respectively.

Chronic toxicity

The toxicity after repeated administration was determined in rats and beagles. For this purpose, the animals were given on 29 and 28 (resp.) successive days 3 dosages of the agent (4.5; 36; 288 mg/kg of body weight). In rats, apart from local effects caused by the application (inflammatory processes at the injection site) no unwanted effects occurred. In dogs, with the two lower dosages, no effects occurred. With the highest dosage, slight changes on cornea and renal tubules were observed, the pathological importance of which is not known. No cases of death occurred.

Mutagenicity

Oxaceprol was extensively tested with regard to mutagenic properties. No indications of any mutagenic potential were found.

Carcinogenicity

There don't exist any tests on carcinogenicity; from bio-assays and clinical tests there didn't result any indications of a tumorigenic potential.

Reproduction

In rabbits, with the highest dosage of 288 mg/kg of body weight, teratorgenic effects were observed - which, however, were not reproducible in a second, identically conducted study. There don't exist any data on the placentar transportation of Oxaceprol in humans nor data on the transition into mother's milk.

c) Pharmacokinetic properties

absorption

3.5 hours after oral application of Oxaceprol there are maximal plasma levels. The bio-availability after oral administration amounts to about 30%.

Distribution
Due to is aqueous solubility, Oxaceprol is distributed in the whole organism. It permeates into the sinovial liquid. No plasma-protein bond has been proved. There are no indications of a cumulation.

Elimination
After IM or IV application the elimination half-time amounts to an average of 2 hours. The elimination occurs exclusively by renal way. The excretion is unchanged and complete. Oxaceprol is neither incorporated nor metabolised.

14. Other indications
Doesn't apply.

15. Indications on stability
AHP 200® film-coated tablets have a shelf life o f 3 years. After the expiration date the drug may not be used any more.

16. Indications on storage
none

a) Indication on waste disposal
Unused rests o f the drug need not be taken to a separate waste disposal.

17. Presentation and package sizes
100 film-coated tablets (N3)
300 film-coated tablets

18. State of information
March 1999

19. Name or company and address of the pharmaceutical business
Producer/pharm. business:
Chephasaar
Chem.-pharm. FabrikGmbH
Mühlstrasse 50
D-66386 St. Ingbert
tel.: (0 68 94) 971 - 0
fax: (0 68 94) 971 - 199

Co-distributor:
Rosen Pharma GmbH
D-66377 St. Ingbert

Distributor:
MIP Pharma GmbH
D-66386 St. Ingbert

Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, NY 10022

Telephone: 212 319-5353
Facsimile: 212 421-1283

Rec'd
1/9/01

KYOWA

January 5 , 2001

Office of Special Nutritionals
HFS-800-820
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

RE: **New Dietary Ingredient Notification**

2'ND COPY

N-Acetyl-L-Hydroxyproline

New Dietary Ingredient Notification

Kyowa Hakko U.S.A., Inc.
599 Lexington Avenue, Suite 4103
New York, NY 10022

Telephone: 212 319-5353
Facsimile: 212 421-1283

KYOWA

January 5 , 2001

Office of Special Nutritionals
HFS-800-820
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

RE: **New Dietary Ingredient Notification**

To whom it may concern:

As specified in the Code Of Federal Regulations, Chapter 21 CFR, Part 190- Dietary Supplements; Subpart B, Paragraph 190.6 for Requirement for Premarket Notification we are submitting information about Kyowa Hakko Kogyo Co. Ltd.'s ingredient product **N-Acetyl-L-Hydroxyproline**.

Our intention with this notification is to exhibit to the addressee that **N-Acetyl-L-Hydroxyproline** (AHYP), an ingredient, is reasonably expected to be safe. Following the format of the CFR notification requirements for paragraph ***(a)***, we supply answers for the requested details as follows.

(1) Name and address of manufacturer: Kyowa Hakko Kogyo Co., Ltd.
Bio Chemicals Company
(a unit of Kyowa Hakko Kogyo Co., Ltd.
1-6-1 Ohtemachi
Chiyoda-ku, Tokyo 100-8185
Japan

Manufacturing site: Kyowa Hakko Kogyo Co., Ltd.
2548 Fujimagari Ube-Shi
Yamaguchi-Ken
Japan 755-8501

(2) The name of the new dietary ingredient is **N-Acetyl-L-Hydroxyproline**.
(3) A description of the dietary supplement. Not applicable.
(i) The level of the new dietary ingredient within a supplement will be in the range of 50 mg to 200 mg per tablet or capsule.
(ii) The conditions of use can be taken daily via oral administration with daily intake of 100 mg to 900 mg with single oral doses taken three to eight times per day.

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KYOWA

Office of Special Nutritionals
HFS-800-820
Center for Food Safety and Applied Nutrition
Food and Drug Administration

(4) The history of use and other evidence of safety.
In our efforts to explain the long use and well documented history of AHYP we have assembled a descriptive "paper" outlining the market of AHYP and the manufacturing of AHYP by Kyowa Hakko, pharmacology, safety and effects in various modes. Refer to table of contents for highlighted details.

Also for your review we enclose copies of the specific references supporting the statements within the "paper". We believe the "paper's" statements and the supporting documents should be sufficient. You will see that some references are written in German, French or Italian whereby there are summaries noted in English and/or are included within the context of the "paper".

We hope that this notification in total should be sufficient to meet FDA requirements for premarket notification; however, if there are additional explanations or further translations needed then please contact the undersigned accordingly.

(5) The signature of the person designated by the manufacturer (Kyowa Hakko Kogyo Co., Ltd.) of the ingredient is:

Neil C. Sullivan

Thank you in advance for your attention and considerations in this matter. We look forward to receiving acknowledgment from the FDA that this notification has been duly received.

Sincerely,

Neil C. Sullivan
Kyowa Hakko USA, Inc.

January 5, 2001

N-Acetyl-L-hydroxyproline

(AHYP-KYOWA)

A new dietary ingredient.

Kyowa Hakko USA, Inc.

January 5, 2001

AHYP-Kyowa / New Dietary Ingredient Notification

CONTENTS

January 5, 2001

1. PREFACE

This booklet describes an overview about *N*-Acetyl-L-hydroxyproline (AHYP) to help understand why this compound is thought to be an ideal candidate for a new dietary supplement that acts on the treatment of arthritis.

AHYP has been used widely in France and Germany as a drug named "Oxaceprol" for the treatment of osteoarthritis, a degenerative joint disease, for over twenty years. The preferential effects of AHYP have been confirmed in various studies on humans and experimental animals. Though the mechanisms of action of AHYP are not well understood, recent research suggests that the inhibition of neutrophil leukocyte infiltration into the synovial membrane and periarticular soft tissue is involved.

Orally administered AHYP is readily absorbed by the body and gradually secreted into urine and feces without being metabolized. Through the extensive clinical experience with AHYP, its potential side effect is found mild and only seen in rare cases.

2. ABBREVIATIONS

AHYP□F*N*-Acetyl-L-hydroxyproline

3. EXPECTED MARKET OF AHYP / MANUFACTURING OF AHYP BY KYOWA

In the market of dietary supplement, the combined formula of glucosamine sulfate and chondroitin sulfate is quite popular as the one targeting those suffering from arthritis. Since the effectiveness and the safety of AHYP has been proved at pre-clinical and clinical stages, AHYP is expected to be one of the highly potential compound or formula in nutraceuticals market.

Kyowa Hakko Kogyo Co., Ltd. has established a patented, unique technology by which hydroxyproline is produced by a carefully controlled fermentation with purified low-molecular weight natural compounds as reaction substrates, followed by chemical modification to yield AHYP (AHYP-KYOWA). In contrast to other commercially available hydroxyprolines, all of which are made from extracted collagen from cow or porcine origin, AHYP-KYOWA is completely free from possible pathogenic contaminants such as viruses and prions. We are currently expanding the production scale of our standardized AHYP-KYOWA to the industrial scale supply it into the huge market of nutraceuticals worldwide.

January 5, 2001

4. PHARMACOLOGY AND SAFETY STUDY ON AHYP

PHARMACOLOGY

In Beagle dogs that were orally administered with ^{14}C-AHYP (10mg/kg), peak plasma level of ^{14}C-AHYP was obtained between 2 and 2.5 hr after administration. Cumulative excretion of ^{14}C-AHYP in those dogs was 60.3% into urine and 41.7% into faeces at 24hr after administration. TLC and autoradiographical analysis of the plasma withdrawn from the dogs 2.5hr after ^{14}C-AHYP administration showed that AHYP was not metabolized. The unlikelihood of AHYP's being a substrate of hydroxyproline oxidase can explain this result. (Lachmann G et al .: Pharmacokinetics and metabolism of ^{14}C-Oxaceprol in beagle dogs after intramuscular and oral administration. *Arzneimittel-Forschung*, 40, 200-6 (1990)).

Therefore, over 50% of the ingested AHYP is thought to be readily moved into the blood stream and completely excreted from the body within a couple of days without being metabolized.

SAFETY DATA

Pharmaceutical preparation of AHYP, Oxaceprol, is formulated as tablets or capsules, each contains 200mg of AHYP. Patients are recommended to take a tablet or a capsule 3 times a day. Unlike most anti-inflammatory drugs such as NSAIDs that are widely used for the treatment of arthritis, AHYP do not have considerable side effects at the prescribed dosages. The extensive clinical experience of AHYP proved its safety on the long-term therapy.

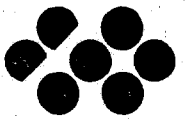
The product description issued by Chephasaar Chem-pharm Fabric GmbH describes the following information about the pharmacological and toxicological properties of AHP200 (Oxaceprol). The original texts are written in German.

Pharmacological properties

Oxaceprol shows a distinct antiphlogistic and analgesic efficacy.

In preclinical studies the antiphlogistic efficacy has been tested with an excellent result in various models (carrageenine paw edema, anaphylactic joint test, carrageenine-induced pleurisy, adjuvant-arthritis) and in comparison to reference antiphlogistics (indomethacin, ASA, phenylbutazone, ibuprofen). These data have also been confirmed with a pyrexal erythema in the human model.

The analgesic efficacy has been shown by the Randall-Selitto and the



Phenylchinone-Writhing-test.

Clinically Oxaceprol has been tested in various indication fields of degenerative joint diseases. In placebo-controlled studies as well as double-blind and randomized studies against ibuprofen and diclofenac the substance has been applied in the therapy of gon-, cox- and spondyl-arthrosis. While the cross-over test versus placebo showed the significant superiority of Oxaceprol, the substance in equal to ibuprofen and diclofenac in its symptomatic efficacy.

In the therapy of rheumatoid arthritis Oxaceprol shows a tendency of superiority to diclofenac.

In all indication fields the typical pain parameters (e.g. pain when starting to move, rest pain and pain following exercise), but also inflammation and flexibility parameters were distinctly improved.

Toxicological properties

Acute toxicity

When orally administered, the LD_{50} in rats is 7,751 mg/kg of body weight, in mice 5,688 mg/kg of body weight; when IM-applied in rats and mice, respectively, it was more than 4,000 mg/kg and 2921 mg/kg of body weight respectively.

Chronic toxicity

The toxicity after repeated administration was determined in rats and beagles. For this purpose, the animals were given on 29 and 28 (resp.) successive days 3 dosages of the agent (4.5; 36; 288 mg/kg of body weight). In rats, apart from local effects caused by the application (inflammatory processes at the injection site) no unwanted effects occurred. In dogs, with the two lower dosages, no effects occurred. With the highest dosage, slight changes on cornea and renal tubules were observed, the pathological importance of which is not known. No cases of death occurred.

Mutagenicity

Oxaceprol was extensively tested with regard to mutagenic properties. No indications of any mutagenic potential were found.

Carcinogenicity

There don't exist any tests on carcinogenicity; from bio-assays and clinical tests there didn't result any indications of a tumorigenic potential.

Reproduction

In rabbits, with the highest dosage of 288 mg/kg of body weight, teratogenic effects were observed – which, however, were not reproducible in a second, identically

conducted study. There don't exist any data on the placentar transportation of Oxaceprol in humans nor data on the transition into mother's milk.

Other given information includes the side effects of Oxaceprol.

Side effects

Under the treatment with Oxaceprol occasionally there have been observed: gastrointestinal complaints, such as nausea, impaired appetite, pain in the stomach or diarrhea, which are often of a passing nature. Seldom there may occur allergic reactions (a reddening of the skin, an itching of the skin, exanthemae). In exceptional cases the following reactions of allergic genesis were described: loss of hair, arthralgia, vasculitis, urticaria, giant urticaria, allergic eosinophilia.

5. EFFECTS OF AHYP *IN VITRO*

1. Effect of Oxaceprol on the structure of proteoglycans synthesized by articular chondorocytes from calves. *Revue du Rheumatisme et des Maladies Osteo-Articulaires*,58(9):629-34 (1991)[1]

- AHYP (170μg/ml) did not affect the structure of proteoglycans synthesized by calf articular chondrocytes with respect to their hydrodynamic sizes, capacity to interact and form aggregates with hyaluronic acid and the length and composition of their glycosaminoglycan side chains.

2. Effect of Oxaceprol on the synthesis and degradation *in vitro* of proteoglycans and proteins by calf articular cartilage explants. *Revue du Rheumatisme et des Maladies Osteo-Articulaires*,57(7-8):579-83 (1990)[2]

- AHYP stimulated the incorporation of $^{35}SO_4$, which indicates proteoglycan synthesis, was observed at concentrations 10^{-6} M (170ng/ml) to 10^{-9} M (170pg/ml) in the culture of calf articular cartilage explants. However, no significant effect was seen on the protein and proteoglycan catabolism at concentrations 10^{-4} M (17μg/ml) to 10^{-9} M (1.7ng/ml).

3. The inhibitory effects of antirheumatic drugs on the activity of human leukocyte elastase and cathepsin G. *Inflammation Research*. 45(7),324 (1996)[3]

- AHYP (10^{-4}M) did not inhibit the activity of human leukocyte elastase and cathepsin G which play a critical role in articular cartilage degeneration.

4. Autoradiographic Investigation of the influence of Oxaceprol on the metabolism of

the Joint Cartilage *In vitro* and *In vivo.Z.Rheumatol.*46(3),136(1987)[4]

- In cultured joint cartilage tissue of hens, AHYP (10μg/ml) stimulated the uptake of ^{3}H-glucosamine and ^{3}H-proline in chondrocytes and enhanced the incorporation of ^{3}H-proline into the macromolecular structures of the cartilage matrix. After *in vivo* intra-articular injection of AHYP into the knee joints , a significant increase of intracellular glucosamine uptake was observed.

5. Effects of Various Antirheumatic Agents on the activity of collagenases. *Pharm.Unserer Zeit*,20(3),118 (1991)[5]

- AHYP did not inhibit collagenase activity.

6. Effect of Nonsteroidal anti-inflammatory drugs on the activity of Elastase and Cathepsin G from human polymorphonuclear leukocytes. *Arzneim.Forsch*,39(10),1208 (1989)[6]

- AHYP (10^{-3}M to 10^{-6}M) did not inhibit elastase and cathepsin G from human polymorphonuclear leukocytes.

6. EFFECTS OF AHYP IN ANIMAL EXPERIMENTS

Some patents have been filed for the anti-inflammatory and wound-healing activity of AHYP (Brit. Pat.1246141 (1971), P.Coirre.,U.S.Pat.3891765(1975) and 3932638(1976), Franco Chimie)[7].

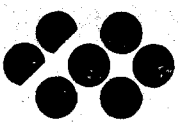
1. Effects of Oxaceprol on the microcirculation in ischemia/reperfusion injury. *European Journal of Medical Research* 3(4):182-8, (1998)[8]

- In the microcirculation of striated skin muscle of Syrian golden hamster, 45min continuous infusion of AHYP (50mg/k) resulted in a significant decrease in postischemic leukocyte adherence after 0.5h and 2h of reperfusion. The histological sections revealed a significant reduction in the number of extravasated leukocytes.

2. Pharmacokinetics and metabolism of ^{14}C-Oxaceprol in beagle dogs after intramuscular and oral administration.*Arzneimittel-Forschung*,40.200-6,(1990)[9]

- Pharmacokinetics of AHYP as stated in **4.** PHARMACOLOGY AND SAFETY DATA ON AHYP

3. *N*-Acetyl-Hydroxyproline effect on the development of experimental intermediary burns in rabbits. *Revue Europeenne d Etudes Cliniques et Biologiques*. 17(6):625- 9.(1972)[10]



- Rabbits with necrotic burns of the flank were fed, during the period of scarring, 20 or 100ng doses of AHYP mixed in the diet. The inflammatory changes and skin healing were not altered by this treatment. However, the scar reduction in the initially burnt zone was less although the quantity of collagen in the scar was increased.

4. Prevention with *N*-Acetyl-hydroxyproline on the toxic cellular effects of nicotine. *Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales.* 65(7):1549-54 (1971)[11]
- AHYP (0.2-0.4mg/ml) prevented cellular toxicity of nicotine on KB cells and rat embryonic fibroblasts in culture.

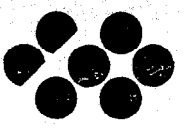
5. Oxaceprol, an atypical inhibitor of inflammation and joint damage. *Pharmacol.Res.*, 33(6): 367-73 (1996)[12]/ Oxaceprol, an atypical inhibitor of inflammation and joint damage. *Z.Rheumatol.*, 55(1):58(1996)[13]/ Oxaceprol, an atypical inhibitor of inflammation and joint damage. *Z.Rheumatol.*, 55(1):118(1996)[14]
- AHYP had no effect on macrophage prostaglandin E_2 release *in vitro* and inhibited carrageenan paw oedema at 18-150 mg/kg p.o.. AHYP (6-54mg/kg/day p.o.) given therapeutically had no effect on the primary paw oedema response, but inhibited secondary lesions in the ears and tail. Histologically, AHYP markedly inhibited inflammatory cell infiltration and bone damage in the adjuvant-injected paw.

6. Effects of *N*-Acetyl Hydroxyproline (Oxaceprol) on an Experimental Post-Contusive Model of Osteoarthritis. A pathological study. *J.Drug Dev.*,3(3),135-42 (1990)[15]
- Orally administered AHYP (25mg/kg/day for three months) was effective in an experimental post-contusive model of osteoarthritis in rabbits which was produced by a blow to the patella with an iron weight of 1kg dropped twice through a cylindric guide 1 meter in length.

7. EFFECTS OF AHYP IN HUMAN STUDIES

The preferential clinical effect of AHYP on osteoarthritis and rheumatoid arthritis has been reported as in the following references.

- Clinical studies of use in degenerative joint disease : R.Schubotz, L.Hausmann, *Therapiewoche* 27, 4248 (1977)[18]



- The conservative treatment of Gonarthrosis with Oxaceprol. *Therapiewoche*, 36(2),116(1986) [19]

  32 patients with gonarthrosis of different degrees had been treated for 6 weeks with Oxaceprol only. The pain at rest was controlled after a 3 weeks therapy and the circle of the joint reduced during 3 weeks on an average of 0.7 cm and was diminished for further 3 weeks of therapy. Restricted mobility of the joint improved. Only 36% of patients had slightly pain when staring after the 6 weeks treatment and the pain-free walking-time increased by a factor 5. The therapy was in 80% successful. The tolerance was good and side effects had not been noted.

- Therapy of Coxarthrosis and Gonarthrosis with Oxaceprol. *Therapiewoche*, 36 (29), 3076 (1986) [20]

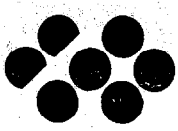
  A total of 50 patients suffering from osteoarthritis of the hip and knee joints received Oxaceprol at a dose of 200mg, 3 times daily for a duration of a 8 months. Treatment with Oxaceprol led to pronounced diminution of pain and reduction of intake of analgesics. Improvement was also noted in the course of treatment with regard to morning stiffness, severity and duration of pain and joint function. The tolerance was good. No adverse reactions had been observed.

- Therapy of chondropathia patellae with Oxaceprol. *Therapiewoche*, 35(28), 3388 (1985) [21]

  367 patients with chondropathia patellae of different degrees have been treated for 8 weeks with Oxaceprol. During the therapy parameters like pain and mobility were significantly improved. In 93.2% of all cases it was possible to restrict the drug treatment exclusively to Oxaceprol. There were no serious adverse reactions under the Oxaceprol therapy, only in a few cases light gastrointestinal disturbances were noticed.

- Therapy of Gonarthrosis with Oxaceprol. *Therapiewoche*, 35(1), 51 (1985) [22]

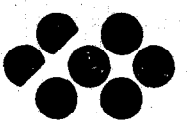
  509 patients with gonarthrosis of different degrees have been treated for up to 8 weeks with Oxaceprol. During the therapy parameters like pain and mobility were significantly improved. The consumption of nonsteroidal anti-rheumatic drugs was strongly reduced. In 75.1 of all cases it was possible to restrict the drug treatment exclusively to Oxaceprol.



- A pragmatic trial of Oxaceprol 200mg in the long-term treatment of lower limb osteoarthritis.*Sem.Hop.*74,47-54(1988)[24]
- Clinical studies of use in several rheumatic conditions: P.Grellat, *Rheumatologie* 27, 223 (1975)[25]
- The acetyl-hydroxyproline, metabolic harmonization of connective tissue(100 cases in rheumatologic practice).*Bordeaux Medical.*3(12),3059(1970)[26]
- Interaction of Fluindone with Oxaceprol.*Therapiewoche*,45(2),162(1990)[27]
- Treatment of rheumatoid arthritis. Comparative study of Oxaceprol versus diclofenac. *Therapiewoche*, 46 (30), 1666-69 (1996)[28]
- Antirheumatic agents and leukocyte recruitment. *Biochemical Pharmacology*, 58, 209-215(1999)[29]

Some preferential effects of AHYP on diseases other than arthritis have also been reported e.g. in the following papers.

- Clinical studies of use in treatment of burns, tumors and other wounds: Y.Privat, *Gaz. Med. de France* 84, 618 (1977)[31]
- Action of *N*-Acetyl-hydroxyproline in the treatment of cutaneous ulcerative lesions. *Annali Italiani di Chirurgia*. 51(5), 527 (1979)[35]
- Prevention of certain acute and chronic effects of nicotine by *N*-Acetylhydroxyproline.□@*Pathologie Biologie*. 19(9), 497 (1971)[36]
- Study of a physiologic regulator of cicatrization (*N*-Acetyl-hydroxyproline). Apropos of 15 clinical cases.*Bordeaux Medical.*4(2),541(1971)[37]



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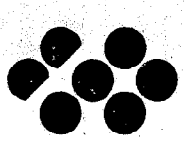

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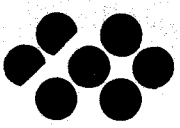

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