Annales

Examen de qualification en vue de l’inscription sur la liste des personnes qualifiées en propriété industrielle

Mention brevets d’invention

Session 2018

AVERTISSEMENT

L'Institut National de la Propriété Industrielle publie pour chaque session d'examen des annales destinées à donner aux candidats une base pour leur formation.

Ces annales regroupent les textes des épreuves écrites de l'examen. Un exemple de réponse fourni par un candidat est présenté. Les réponses n'ont été ni améliorées, ni corrigées. Sans être nécessairement parfaites à tous points de vue, elles constituent un échantillon de copies ayant obtenu une note sensiblement supérieure à la moyenne.

Un exemple de sujet pour l'épreuve orale est également proposé.

Ces annales sont publiées par secteur technique.

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Cet examen est mis en place conformément à l'arrêté du 23 septembre 2004 modifié portant application des dispositions des articles R.421-1, R.421-2 et R.421-5 à R.421-8 du code de la propriété intellectuelle.

Sommaire

Instructions aux candidats

PREMIERE EPREUVE ECRITE

Dans cette épreuve, le candidat doit supposer qu'il a reçu de son client le courrier annexé au sujet, qui comporte la description d'une invention pour laquelle son client souhaite obtenir un brevet français, ainsi que des renseignements et/ou documents relatifs à l'état de la technique le plus pertinent dont son client a connaissance.

Le candidat doit accepter les faits exposés dans le sujet de l'épreuve et fonder ses réponses sur ces faits. Il décide sous sa propre responsabilité s'il fait usage de ces faits, et dans quelle mesure.

Le candidat doit admettre que l'état de la technique, dans le domaine spécifique de l'invention que lui soumet son client, est effectivement celui qui est indiqué dans l'épreuve et/ou ses documents annexes, et que cet état de la technique, le cas échéant complété des connaissances générales nécessaires sur lesquelles il pourrait s'appuyer de façon implicite, est exhaustif.

Il est demandé au candidat de rédiger sauf instruction contraire, en les présentant dans cet ordre : (1) la partie introductive de la description de la demande de brevet souhaitée par le client, et (2) un jeu de revendications comprenant au moins une revendication indépendante et quelques revendications dépendantes.

Il est entendu par partie introductive :
- L'indication du domaine technique auquel se rapporte l'invention ;
- L'indication de l'état de la technique antérieure, connu du demandeur, pouvant être considérée comme utile pour l'intelligence de l'invention et pour l'établissement du rapport de recherche ; les documents servant à refléter l'état de la technique antérieure sont, autant que possible, cités ;
- Un exposé de l'invention, telle que caractérisée dans les revendications, permettant la compréhension du problème technique ainsi que la solution qui lui est apportée ; sont indiqués, le cas échéant, les avantages de l'invention par rapport à l'état de la technique antérieure.

La ou les revendication(s) indépendante(s) sera(ont) rédigée(s) de façon à donner au client la protection la plus étendue possible, tout en respectant les critères de brevetabilité et les exigences formelles applicables.

Les revendications dépendantes, seront rédigées de façon à définir une position de repli utile pour le cas où un art antérieur affectant la généralité de chaque revendication indépendante serait découvert après le dépôt de la demande brevet.

L'exercice de rédaction demandé se limite à une seule demande de brevet français, qui devra satisfaire aux exigences d'unité d'invention. Au cas où, dans la pratique, il demanderait la protection d'autres inventions en déposant une ou plusieurs autres demandes distinctes, le candidat devra indiquer succinctement, dans une troisième partie, l'objet de la principale revendication indépendante de chaque autre demande distincte, la rédaction détaillée de telles revendications indépendantes n'étant cependant pas requise.

Enfin le candidat peut, sauf instruction contraire du sujet, indiquer dans une note séparée les raisons du choix de sa solution, et par exemple expliquer pourquoi il a choisi telle ou telle forme de revendication, telle ou telle caractéristique pour une revendication indépendante, tel ou tel élément particulier de l'état de la technique comme point de départ, toute note de ce genre devant cependant rester brève.

SUJET DE LA PREMIERE EPREUVE ECRITE

Vous trouverez, ci-joint, une note technique transmise par votre client, la société BIOPURE, spécialisée dans le domaine des compléments alimentaires à base d'extraits végétaux.

Une recherche d'antériorités a été effectuée par votre client et a permis d'identifier les documents D1, D2 et D3 de l'état de la technique.

Après avoir pris connaissance de l'ensemble des documents, vous procéderez à la rédaction de la partie introductive et d'un jeu de revendications d'une demande de brevet français protégeant au mieux les intérêts de votre client tout en respectant les critères de brevetabilité et les exigences formelles applicables.

Dans une note à votre client, vous pourrez lui indiquer les raisons du choix de la solution retenue. Vous lui ferez également part de toutes vos suggestions et le cas échéant, répondrez succinctement aux questions posées dans la note technique.

Si vous estimez que plus d'une demande de brevet est nécessaire pour protéger au mieux les intérêts de votre client, vous indiquerez brièvement, dans une troisième partie, l'objet de la principale revendication indépendante de chaque autre demande distincte, la rédaction détaillée de telles revendications indépendantes n'étant cependant pas requise.

Annexes :

Note technique + plaquette publicitaire
D1 : GB2,222,222 ;
D2 : US5,200,000 ;
D3 : Fiche Conseil AZ : huile végétale de pépins de tomates.

Montreuil-Bellay

Le 25 juin 2018

Madame, Monsieur,

Comme nous vous l'avons indiqué lors de notre entretien téléphonique, notre société BIOPURE est spécialisée dans la préparation et la commercialisation de compléments alimentaires à base d'extraits végétaux.

Nous nous apprêtons à lancer une gamme à activité bronzante et comme vous nous l'avez conseillé, avant le lancement, il serait prudent de déposer une demande de brevet.

Nous vous transmettons donc tous les éléments en notre possession.

Tout d'abord voici une explication sur le phénomène de la pigmentation de la peau :

La pigmentation cutanée des mammifères, en général, et de l'homme en particulier, repose sur la biosynthèse d'un pigment azoté, la mélanine, à partir de tyrosinase, dont la régulation est sous l'influence de plusieurs paramètres :

- la tyrosinase, produite par la cellule pigmentaire,

- le mélanocyte, qui sous l'influence de la lumière ultraviolette, catalyse l'oxydation de la tyrosine en dihydroxyphénylalanine (DOPA), puis en dihydroxyindole et enfin en mélanine,

- la mélanine peut ensuite subir des polymérisations oxydatives qui vont accentuer sa coloration ; ce pigment est présent sous la forme d'organites, les mélanosomes, dans les dendrites des mélanocytes précités et ces mélanosomes sont ensuite transmis aux kératinocytes, qui vont transporter la mélanine jusqu'à la surface de la peau où elle sera éliminée progressivement lors de la desquamation naturelle.

La mélanine formée est composée de deux types :

(1) l'eu-mélanine, qui est d'une couleur brun-noir et se forme par polymérisation de produits d'oxydation de la dopaquinone et (2) la phéo-mélanine, qui est d'une couleur brun-roux et se forme par polymérisation de dérivés soufrés de la dopaquinone.

La couleur de la peau et son intensité dépendent donc du contenu des kératinocytes en mélanine, du type de mélanine présente dans les kératinocytes, de la vitesse de desquamation de la peau et de l'épaisseur de la couche cornée qui est la couche contenant le plus de pigment.

Essentiellement pour des raisons esthétiques, en Occident, l'homme s'expose de plus en plus au soleil, pour avoir une peau bronzée. Or les radiations ultraviolettes (UVA et UVB), qu'elles proviennent des rayonnements du soleil ou de lampes à bronzer, présentent des dangers pour la santé et entraînent un vieillissement prématuré de la peau.

C'est pourquoi, les consommateurs sont de plus en plus intéressés par des produits qui procurent à la peau une coloration proche de celle d'un bronzage naturel sans pour autant qu'il soit nécessaire de s'exposer à des rayonnements ultraviolets.

Il ressort de diverses études publiées ces dernières années que les caroténoïdes présentent la propriété d'induire la synthèse de mélanine. De ce fait, lorsqu'ils sont ingérés par voie orale, ils

permettent de conférer à la peau une coloration proche de celle d'un bronzage naturel habituellement obtenu par une exposition au soleil ou sous une lampe à bronzer.

Nous avons deux formulations prêtes pour une commercialisation dès le début de l'été. Nous vous joignons la plaquette publicitaire pour la composition spécialement adaptée à l'été. Comme vous le verrez, nous surfons sur la vague des produits d'origine naturelle apportant une grande sécurité pour les consommateurs.

Pour d'autres applications, nous avons déjà utilisé des extraits de divers fruits et légumes comme les raisins, les carottes, les tomates, les poivrons rouges, le melon, les abricots, les pêches, les agrumes tels que l'orange et le pamplemousse rose.

Ces extraits paraissent adaptés à une gamme de compléments alimentaires à activité bronzante en raison de leurs teneurs en caroténoïdes.

Les caroténoïdes sont des pigments colorés synthétisés essentiellement par les végétaux pour se protéger de la lumière et accomplir leur photosynthèse ; ils donnent leur couleur vive aux fruits et légumes tels que les carottes, poivrons rouges, abricots, melon, …

Les caroténoïdes sont apportés à l'homme exclusivement par l'alimentation.

Les caroténoïdes comprennent les carotènes tels que notamment l'alpha-carotène, le beta-carotène et le lycopène, et les xanthophylles telles que la zéaxanthine, la lutéine, la cryptoxanthine.

Notre société a isolé certains mélanges de caroténoïdes à partir des extraits de fruits et légumes que nous avions déjà utilisés. Les compositions massiques de ces mélanges particuliers de caroténoïdes sont données ci-après.

Pour le moment nous ne souhaitons pas divulguer le procédé que nous avons mis en œuvre afin d'isoler ces mélanges de caroténoïdes de nos extraits végétaux.

Les mélanges de caroténoïdes issus d'extraits de carotte ont la composition massique (%) suivante :

beta-carotène	30
zéaxanthine	10
cryptoxanthine	20
lutéine	40

Les caroténoïdes issus des extraits de pépin de tomate contiennent exclusivement du lycopène et aucun autre caroténoïde.

Les caroténoïdes des extraits de melon contiennent 50% de lycopène, 50% de zéaxanthine et aucun autre caroténoïde.

Les caroténoïdes des extraits de poivrons rouges ne contiennent pas d'alpha-carotène mais du beta-carotène entre 2 et 20%, de 5 à 10% de cryptoxanthine et 2 à 10% de lycopène, le reste étant de la lutéine.

Les mélanges de caroténoïdes des extraits d'abricots ont la composition massique (%) suivante:

beta-carotène	18,6
alpha-carotène	11,4
cryptoxanthine	30
lutéine	40

Les mélanges de caroténoïdes des extraits de pêche ont la composition massique (%) suivante :

beta-carotène	10
alpha-carotène	20
cryptoxanthine	25
zéaxanthine	45

Comme nous vous l'avions indiqué, nous avons préparé plusieurs formules que nous avons fait tester sur des volontaires soumis à une stricte confidentialité.

Les formules que nous avons préparées sont des compositions liquides introduites dans des capsules semi solides destinées à être ingérées. Elles pourraient également être administrées sous forme de gélules, sirop, gouttes. Des formules sèches type comprimés pourraient également être envisagées sans difficulté technique.

De préférence, pour obtenir l'effet esthétique recherché, les compositions sont administrées à raison de 1 ou 2 capsules / jour, préférentiellement en une seule prise.

La base de formulation des compositions selon l'invention est tout à fait classique. Elle peut comprendre tout excipient adapté à une administration par voie orale, en particulier des huiles végétales neutres telles que de l'huile de soja hydrogénée, de l'huile de blé, de l'huile de pépin de raisin, de l'huile de tournesol, de l'huile de sésame, etc…

La base de formulation peut en outre renfermer des vitamines et/ou des oligo-éléments. Les vitamines sont de préférence choisies parmi les vitamines ayant une action bénéfique sur la peau et telles que par exemple la vitamine B5 (acide pantothénique), la vitamine C (acide ascorbique), la vitamine D (calciférol) et la vitamine E (tocophérols et tocotriénols).

Les compositions unitaires des formules que nous avons préparées et testées sont données ci-après :

Composition 1 :

Base de formulation	190 mg
Caroténoïdes issus d'extrait de carotte	10 mg
Caroténoïde issu d'extrait de pépin de tomate	3 mg

Composition 2:

Base de formulation	190 mg
Caroténoïdes issus d'extrait de carotte	60 mg
Caroténoïde issu d'extrait de pépin de tomate	3 mg

Nous avons aussi préparé et testé des compositions à base des caroténoïdes synthétiques suivants : alpha-carotène, beta-carotène, lycopène, zéaxanthine, cryptoxanthine et lutéine.

Les ingrédients des compositions que nous avons testées sont listés dans le tableau 1 ci-joint :

Les tests ont été conduits de la façon suivante :

Un panel de 160 testeurs présentant un bon état général de santé, à peau claire, a été sélectionné. Ce panel a été divisé en 16 groupes de 10 personnes. A chaque groupe a été attribuée à l'aveugle l'une des compositions 1 à 16, la composition 11 étant la composition témoin.

Les 16 compositions testées ont été conditionnées en capsules semi-solides.

A compter du 15 janvier 2018, pendant 28 jours successifs, chaque personne a ingéré une capsule au petit-déjeuner entre 7h00 et 9h00. Pendant les 25 premiers jours, ils n'ont pas été exposés à la lumière extérieure du soleil ni à des lampes UV. Les 25, 26, 27 et 28ème jours, ils ont été exposés de 11h00 à 11h30 à un rayonnement UV contrôlé et de même intensité pour chacun des membres du panel.

Chaque jour à 14h00, la coloration de leur épiderme (surface de la main droite et front) a été observée.

Les résultats de coloration de la peau sont donnés dans le tableau 2 (une moyenne a été faite sur les 10 testeurs d'un même groupe). L'indice de coloration a été attribué après observation visuelle en comparant avec une échelle de teinte de peau standardisée allant de 1 à 4 (coloration croissante).

Tableau 1:

COMPOSITION (mg)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Base de formulation	190	190	190	190	190	190	190	190	190	190	190	190	190	190	190	190
Alpha carotène			1,4	2,0	2,0	0	0	2,5	2,5	0,5	0	0,2	0,2	2	1,5	0,5
Beta carotène			2,6	0.5	0,5	3	2,0	0	0	1,5	0	0,3	2,8	2	0,5	0,5
Lycopène			2	0	25	0	10	7,5	0	0,4	0	2	5	3	18	2
Zéaxanthine			1	1	1	1	1	1	1	1	0	0	0	0,5	1,5	1
Cryptoxanthine			0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0	1,5	1,5	1	0	0,5
Lutéine			2	2	2	2	2	2	2	2	0	0,5	1,5	2	1	2
Ratio carotènes (α et/ou β)/lycopène			2/1	na (*)	1/10	na	1/5	2/6	na	5/1	na	1/4	3/5	4/3	1/9	1/2

(*) na : non applicable

Nous n'avons pas eu le temps de reporter les valeurs pour les compositions 1 et 2 dans ce tableau, mais vous n'aurez pas de difficultés à les calculer.

Tableau 2

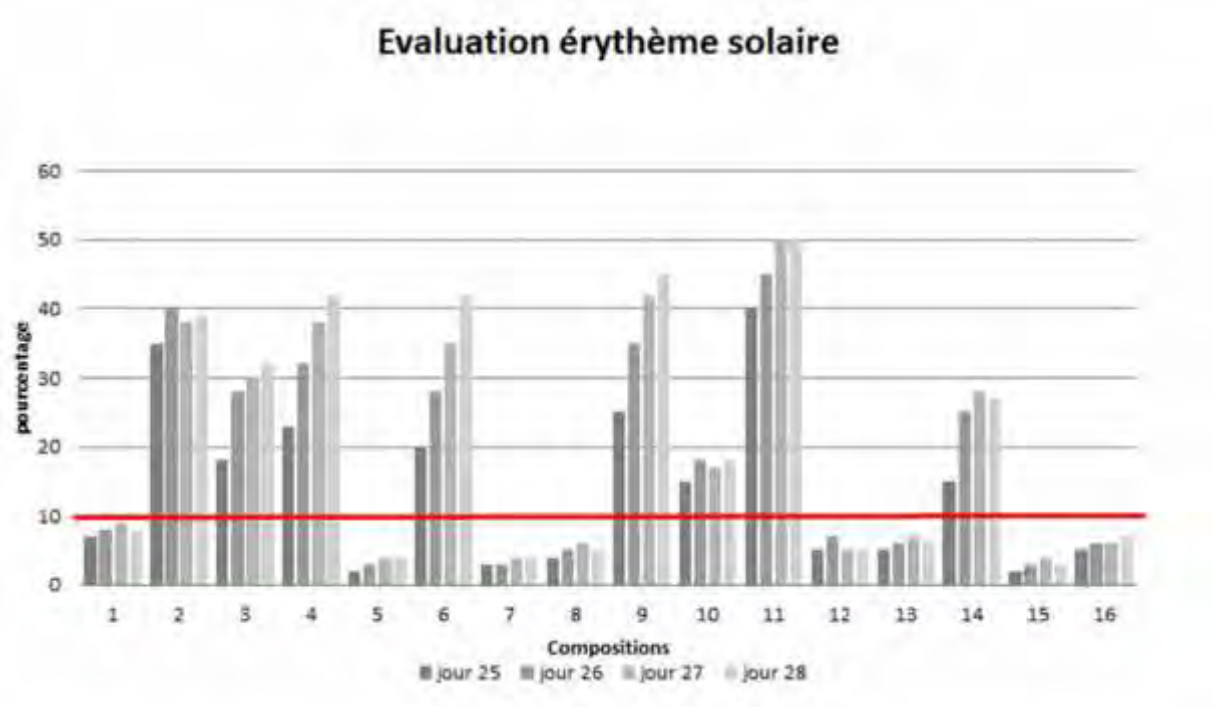
Indice de coloration moyen en fonction du temps en jours (jour 0 = jour précédent la première prise) pour chaque composition testée 1 à 16.

COMPOSITIONS	JOURS																			
	0	5	10	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1	1	1	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4	4	4
2	1	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4
3	1	1	2	2	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4
4	1	1	1	2	2	2	2	2	2	3	3	3	3	3	4	4	4	4	4	4
5	1	1	2	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4	4
6	1	1	1	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4	4	4
7	1	1	2	2	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4	4
8	1	1	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	4
9	1	1	1	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4
10	1	1	2	2	2	2	3	3	3	3	3	4	4	4	4	4	4	4	4	4
11	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4
13	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4
14	1	1	1	1	2	2	2	2	2	3	3	3	3	3	3	3	4	4	4	4
15	1	1	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	4	4
16	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4

Les 25, 26, 27 et 28ème jour, le degré de rougeur et irritation de la peau a été mesuré à 14h00. Ce degré de rougeur et d'irritation traduit les symptômes d'un érythème solaire.

Les résultats sont exprimés en %. Un pourcentage au-delà de 10% est significatif d'un érythème solaire.

Les résultats obtenus sont présentés dans l'histogramme joint.



Nous avons également remarqué que lorsque le contenu des capsules des compositions 3 et 5 est appliqué sur le dos de la main, une coloration apparaît après plusieurs applications. Nous ne vous en avions pas parlé lors de notre entretien téléphonique mais nous nous demandons si cela pourrait présenter un intérêt.

Nous vous signalons également que la législation européenne sur la quantité de carotène (alpha et/ou beta) ingérable par jour va être modifiée. Actuellement elle est de 6 mg/j maximum et va être abaissée à 3 mg/j.

Comme vous nous l'aviez demandé, nous vous envoyons également 3 documents antérieurs (D1, D2 et D3) que nous avons trouvés lors d'une recherche faite préalablement au lancement de nos tests.

Nous espérons vous avoir transmis tous les éléments nécessaires. Nous restons à votre disposition pour toute question.

Bien cordialement,

Mr Beauregard
Directeur R&D de BIOPURE

PJ :
Plaquette publicitaire TEINT D'ETE
D1 : GB2,222,222 ;
D2 : US5,200,000 ;
D3 : Fiche Conseil AZ : huile végétale de pépins de tomates (impression d'une page Internet).

CIP : 234569- juillet 2018

Description:

TEINT D'ÉTÉ de Biopure est un complément alimentaire qui vous donne un joli teint hâlé.
TEINT D'ÉTÉ prépare votre peau au soleil en lui donnant un joli teint hâlé même en l'absence d'exposition
Grâce à sa composition particulière en caroténoïdes, TEINT D'ÉTÉ prévient l'érythème solaire lors de l'exposition au soleil.
A base d'extraits végétaux, TEINT D'ÉTÉ est un produit 100% naturel, issu de l'agriculture biologique
TEINT D'ÉTÉ est entièrement fabriqué dans nos usines de Montreuil-Bellay et bénéficie du label « Fabriqué en France »

Conseil d'utilisation:

Prendre une à deux gélules de TEINT D'ÉTÉ chaque matin pendant 20 à 30 jours avant l'exposition au soleil.
La cure peut être renouvelée jusqu'à 3 fois dans l'année pour garder un teint d'été en toute saison

Composition pour 1 gélule:

Huile de soja hydrogénée	40 mg
Huile de blé	95 mg
Lécithine de soja	20 mg
Tocophérols naturels	5 mg
Acide ascorbique	30 mg
Caroténoïdes issus d'extrait de carotte	10 mg
Caroténoïde issu d'extrait de pépins de tomate	3 mg

(ingrédients issus de l'agriculture biologique)

Conditionnement:

Boite de 30 gélules

(12) UK Patent Application (19) GB (11) 2 222 222 (13) A

(43) Date of A Publication 20.07.1994

(21) Application No 9323333.3

(22) Date of Filing 24.11.1993

(30) Priority Data
(31) 08003333 (32) 13.01.1993 (33) US

(71) Applicant(s)
Slide Company

(Incorporated in USA - California)

United States of America

(72) Inventor(s)

A Furst
B Flopper

(74) Agent and/or Address for Service
Bells & Songs

United Kingdom

(51) INT CL5
A23L 1/301/303, A23P 1/04, A61K 35/78

(52) UK CL (Edition M)
A2B BMDE9 B648 B822 B861 B865 B866
A5B BE B30X B30Y B829
U1S S1313 S2411

(56) Documents Cited

(58) Field of Search
UK CL (Edition M) A2B BMDE1 BMDE9 BMV1 BMV5, A5BBE
INT CL5 A23L, A23P, A61K
ON-LINE DATABASES, WPI, US CLAIMS

(54) Carotenoid food supplement

(57) A diet supplement composition containing powdered, dried fruits and vegetables rich in alpha-carotene, beta-carotene and lycopene encapsulated in a gelatin capsule in an edible oil.

CAROTENOID FOOD SUPPLEMENT

TECHNICAL FIELD

This invention is in the field of food supplements to provide carotenoids at optimal ingestion levels.

BACKGROUND ART

Carotenoids are the most numerous group of pigments in nature. They play a critical role in electron transport reactions in plants and are indispensable to healthy functioning of human beings and most animals. The full extent of their role in physiology is not known but experimental evidence indicates that carotenoids may be necessary for proper functioning of the immune system and for protecting tissue from ultraviolet damage. They may reduce chemically induced neoplasia and malignant cell transformation.

Carotenoids are found in fruits and vegetables and an adequate intake of carotenoids, the amount recommended by government agencies and the medical profession, requires ingestion of far more fruits and vegetables than the average diets of persons in the United States and other nations in the Western culture provide. Among better-known carotenoids are alpha-carotene, beta-carotene and lycopene. In addition to being found in fruits and vegetables, beta-carotene is synthesized and the synthetic compound is commercially available. However, there

are hundreds of lesser-studied carotenoids that are found in fruits and vegetables, hereinafter referred to collectively as vegetables, and those lesser-known carotenoids are not present in synthetic preparations such as beta-carotene. The lesser-known carotenoids may play an important (albeit, not fully explored) role in human health as indicated by illnesses or malfunctioning of persons in the Western culture whose diets do not contain enough vegetables. Many of these illnesses or malfunctions are less frequent among persons in populations where diets include large amounts of vegetables. The beneficial effects of lesser-studied or unknown carotenoids may be due to their direct effectiveness in trace amounts or to catalytic or synergistic effects that they exert with the better-known and more thoroughly studied carotenoids such as beta-carotene. Synthetic carotenoids also lack natural distributions of structural differences in their molecules, such as cis- and trans- forms which occur in natural proportions in vegetables. This phenomenon is observed in many ways. For example, when experimental animals are fed either natural or synthetic beta-carotene, liver analyses show at least ten-fold higher levels of beta-carotene in those animals fed the natural form.

DISCLOSURE OF THE INVENTION

This invention is a composition useful as a dietary supplement which provides adequate carotenoid ingestion to persons regardless of the inadequacy of their diets with respect to their vegetable intake. The composition of this invention not

only provides adequate quantities of known carotenoids to the diet but it additionally provides the natural level of lesser known and even unknown carotenoids so that the ingestion of a full spectrum of carotenoids in naturally balanced proportions is achieved by supplementing the diet with the composition of this invention.

This invention is an encapsulated composition of powdered vegetable material in an edible oil base. The composition comprises vegetable material that provides alpha-carotene, beta-carotene and lycopene in proportion to each other of about 20 percent to about 40 percent alpha-carotene, about 55 percent to about 80 percent beta-carotene, and about 3 percent to about 20 percent lycopene - the percentages being the weight relationships of those three carotenoids to each other. By providing those carotenoids in that proportion from vegetable materials, the whole array of carotenoids in approximately the balanced composition relationships found in the diet is provided in the composition of this invention. Vegetables that contain high quantities of alpha- and beta-carotene do not contain high quantities of lycopene but they have their own array of other carotenoids. However, those vegetables providing high concentrations of lycopene have an array of carotenoids that are different from the other carotenoids in those vegetables providing high quantities of alpha- and beta-carotene. It has been found that supplying a carotenoid content in the proportions noted above from vegetable sources of those carotenoids provides virtually the entire array of carotenoids in the appropriate

distribution to duplicate the carotenoid ingestion from a balanced diet rich in vegetables. The carotenoids contained in vegetables not only include different carotenoids than those produced synthetically but additionally the carotenoids found in vegetables are superior to synthetic carotenoids because they differ in such things as structural distribution - for example, between cis- and trans- isomers.

Different vegetables contain different carotenoids, and even when they contain the same carotenoids they are in different proportions. For example, carrots are perhaps the best known source of beta-carotene but they contain no lycopene, while tomatoes are a rich source of lycopene but contain very little beta-carotene. Spinach is rich in lutein but has no lycopene and relatively little alpha-carotene. Each vegetable also contains an array of carotenoids that are lesser known, and no vegetable contains all of them.

All carotenoids are contained in the lipid portion of vegetables, so there is an option to use oleoresins extracted from vegetables or powdered, dried vegetables in the compositions of this invention. The decision to use powders or oleoresins is usually based on the cost or availability of oleoresins and the need to adjust the texture or viscosity of the composition. Most carotenoids survive carefully controlled processes such as spray-drying, freeze-drying, powdering, and extraction quite well. The composition of this invention, accordingly, provides a level of alpha-carotene, beta-carotene and lycopene that supplements the usual Western-culture diet to provide the proper intake of those

three carotenoids. In addition, the composition of this invention, by being made from vegetable oleoresins and powdered vegetables, contains a whole array of natural carotenoids - those that have never been studied and those that are not known - and even the known carotenoids are provided in the proper structural distribution that one gets from a balanced diet of vegetables.

DETAILED DESCRIPTION OF THE INVENTION

A composition embodying this invention was made having the following ingredients on a weight basis.

Ingredient	Percent
Carrot oleoresin	26.1
Red bell pepper oleoresin	3.0
Peach powder	3.7
Strawberry powder	3.7
Tomato powder	44.9
Spinach powder	14.9
Apricot powder	3.7

The carrot and red pepper oleoresins were obtained by extraction from carrots and red bell pepper bodies respectively. The carrot oleoresin was bright orange, virtually flavorless and readily miscible in water. The red bell pepper oleoresin was a red liquid having the aroma of red bell peppers and very mild red bell pepper flavor.

The powdered material was all obtained by spray- or freeze-drying the noted ingredient and subdividing it to a powder form according to known techniques. The spinach was subjected to low-pressure steaming in a chamber for sufficient time to kill bacteria after which it was freeze-dried and powdered. Dried spinach and dried peach were powdered together to deal with the natural hygroscopicity of peach powder. The carotenoid-containing materials were blended with vegetable oil and lecithin to provide an appropriate texture for encapsulating in a gelatin capsule. The materials were encapsulated in amounts providing 1.5 mg of beta-carotene, 0.5 mg of alpha-carotene and 0.4 mg of lycopene per capsule. The encapsulated materials also supplied other carotenoids that occur naturally in the powders and oleoresins stated in Table 1.

Eleven healthy men and women volunteers between 22 and 52 years of age participated in a study to test if the supplement raised blood carotenoid level. The volunteers had no history of chronic disease, they were taking no medications, they did not smoke, and they were all within 10 percent of ideal body weight for their heights. None of the volunteers had an unconventional dietary pattern, such as vegetarianism. Those volunteers who had been taking carotene-containing supplements stopped doing so two weeks before the study began. All of the volunteers were evaluated for such factors as weight, blood pressure, pulse and temperature at the beginning of the study, two weeks after the beginning of the study, and weekly thereafter.

The study lasted six weeks. During this entire time the diets of the volunteers were self-selected from low-carotenoid foods on a list of foods provided to them. The volunteers were also given a list of carotenoid-containing foods that they were to avoid during the study. The recommended daily diets of the volunteers contained less than 0.4 mg of beta-carotene and alpha-carotene and no lycopene. After two weeks on the low-carotenoid diet the volunteers began taking six of the capsules described above daily. This period was called the supplementation period and it continued for the next four weeks.

A fasting blood sample was collected from each volunteer before the beginning of the study to establish a base-line serum carotenoid level for each subject that was characteristic of his or her own diet and physiologic absorption characteristics for carotenoids. The base-lines were for alpha-carotene, beta-carotene and lycopene only. Blood samples were also collected after two weeks on the low carotenoid diet and weekly during the supplementation period. The samples were collected in accordance with recognized medical techniques, centrifuged to obtain plasma, and analyzed for alpha-carotene, beta-carotene and lycopene by the HPLC method of Bieri et al. Table 2 below reports the data resulting from these tests. The columns headed A are the base-line readings of each volunteer at the start of the test. The columns headed B are the readings after two weeks on the low carotenoid diet at which time the supplementation period began. The columns headed C are the readings at the end of the study - that is, six weeks from the

beginning of the study and four weeks from the beginning of the supplementation period. All reported values are in nanograms per milliliter of serum.

TABLE 2

	Beta-Carotene			Alpha-Carotene			Lycopene		
Volunteer	A	B	C	A	B	C	A	B	C
1	1028	526	1065	422	241	541	728	433	302
2	530	371	1346	169	110	617	275	166	263
3	255	120	365	96	50	238	448	285	400
4	981	571	1170	177	125	428	254	151	238
5	73	21	72	80	20	56	180	126	125
6	156	111	377	44	33	240	437	213	172
7	341	290	1222	129	98	419	292	205	354
8	578	238	578	245	141	236	590	232	216
9	630	435	1254	302	154	495	453	316	343
10	302	169	907	110	79	510	780	284	225
11	154	107	204	43	45	145	856	692	724

From Table 2 it is evident that the data establish the general trend that two weeks on a low carotenoid diet significantly diminished the serum alpha- and beta-carotene levels of the volunteers. The data also establish that the composition of this invention taken in the four-week supplementation period restored the serum alpha- and beta-carotene levels to the base-line level or in excess of the base-line level for each volunteer.

The data reporting lycopene levels were less conclusive. In general there was a significant reduction in lycopene levels between the base-line levels and the start of the supplementation period but the supplementation period did not restore base-line levels. However, plasma lycopene levels are known to respond slower to changes in dietary intake than alpha- or beta-carotene levels. Lycopene supplementation initially stabilized lycopene plasma levels preventing further decline. It is hypothesized that if the study had been prolonged, gradual increases in lycopene levels to or in excess of the base-line levels would be observed. The weekly tests for serum lycopene bear out this hypothesis. For all but two of the volunteers there was a rising trend in serum lycopene in the final week of the supplementation period. Specifically, the data for the final week were:

Volunteer	Fifth week	Sixth week
1	312	302
2	220	263
3	174	400
4	168	238
5	20	125
6	135	172
7	101	354
8	77	216
9	281	343
10	274	225
11	705	724

As noted above, the volunteers were healthy persons before the test started. They were also healthy persons after the test ended. They noticed no subjective changes in their health during the six weeks of the test. It is known that serum carotenoid levels are accurate indicators of the availability of these essential compounds for maintaining good health and that temporary periods of low serum carotenoid levels have no affect on the health of the average individual. However, chronic low carotenoid serum levels may cause health deterioration problems. The study demonstrates that regular ingestion of the composition of this invention will maintain serum carotenoid levels even with a diet that is almost devoid of carotenoids. Its regular use will provide a person with significant ingestion of carotenoids regardless of the vegetable content of that person's usual diet.

D1

CLAIMS

1. A composition comprising a suspension of powdered materials in an edible oil, said powdered materials comprising a mixture of dried, vegetables, said composition containing alpha-carotene, beta-carotene and lycopene in proportion to one another on a weight basis of from about 20% to about 40% alpha-carotene, from about 55% to about 80% beta-carotene and from about 3% to about 20% lycopene.

2. The composition of claim 1 wherein said edible oil comprises carrot oleoresin.

3. The composition of claim 1 wherein said edible oil comprises red bell pepper oleoresin.

4. The composition of claim 1 wherein said powdered material comprises spinach powder.

5. The composition of claim 1 wherein said powdered material comprises tomato powder.

6. The composition of claim 1 enclosed in a gelatin capsule.

7. The composition of claim 6 wherein said capsule contains from about 500 to about 1000 milligrams of said composition.

8. A composition enclosed in a gelatin capsule comprising from about 150 to about 200 mg of carrot oleoresin, from about 30 to about 50 mg of red bell pepper oleoresin, from about 100 to about 400 mg of powdered, dried tomato, and from about 50 to about 200 mg of powdered, dried spinach.

D2

United States Patent [19]

Shapira

[11] **Patent Number: 5,200,000**

[45] **Date of Patent: Mar. 1, 1994**

[54] **SUN-EXPOSURE NUTRITIONAL SUPPORTING COMPOSITION**

[76] Inventor: **Nina Shariba**, Tel-Aviv, Israel

[21] Appl. No.: 960,000

[22] Filed: **Oct. 16, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 500,000 Jun. 28, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jun. 29, 1989 [IL] Israel 090000

[51] **Int. Cl.**[5] **A61K 47/00**

[52] **U.S. Cl** **424/439**; 424/401

[58] **Field of Search** 424/401, 439; 514/904, 514/775, 725; 426/590, 524

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Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Jacobson, Price, Holman & Stern

[57] **ABSTRACT**

A nutritional soft drink for protection against the danger of exposure to UV light. The drink comprises a mixture of carotenoids, optionally together with vitamin C and/or vitamin E and/or other physiologically acceptable antioxidants in an amount which does not exceed 10 vitamin ARDA equivalents of provitamin A per liter of drink. Other biologically acceptable flavors and/or additives may be added. The drink may be in liquid drinkable form or in frozen or semi-frozen form.

13 Claims, No Drawings

SUN-EXPOSURE NUTRITIONAL SUPPORTING COMPOSITION

This application is a continuation of application Ser. No. 05/500,000, filed Jun. 28, 1990 now abandoned.

The present invention relates to a nutritional soft drink containing carotenoids, which are useful as protecting agents against damages due to exposure to UV light, particularly skin cancer in humans.

It has been known for a long time that UV light is a major cause of skin cancer. The art employs numerous protecting agents against the dangers of exposure to UV light, particularly protective materials to be applied topically to the skin, such as sun ointments and lotions, be they water, alcohol or oil based, which contain photo-protectant materials. This approach—so far the only effective approach widely used and accepted—has the considerable drawback of requiring high amounts of active photo-protectant materials, some of which have recently become suspect of becoming toxic under these conditions and in different ways harmful to health. Furthermore, obtaining a constant and uniform coverage of the skin with protecting ointments is difficult, and also the effectiveness of such protectants to defend the skin against UVA radiation is debatable.

Systemic carotenoids and antioxidants, both with and without Pro-Vitamin A activity, have been known for some time to be effective as protective agents against sun exposure hazards.

Recently, it has been suggested to increase carotenoids consumption by dietary modification or oral administration of carotenoid supplements, e.g., gelatin capsules and/or tablets. The said approach does not provide an optimal regime because appetite is decreased by exposure to sun and heat, and because intake of antioxidants in concentrated form, e.g., by swallowing tablets which should preferably be taken with meals, may expose to uneven dosages of antioxidants which may be associated with metabolic interference and even toxicity.

Such systemic approaches, furthermore, have the considerable drawback of being unsynchronized with the actual exposure to sunlight and therefore unnecessarily high—or ineffectively low—amounts of protective agents can be found in the system.

It is therefore clear that it would be highly desirable to provide a vehicle through which intake of carotenoids and other systemic photo-protectants can be applied in a proportional manner, without substantially exceeding the amount which is necessary for achieving substantial physiological protection from exposure to sun radiation, and/or exceeding the RDA generally accepted safe limitations.

It is an object of the present invention to provide a sun-exposure nutritional supporting drink which contains carotenoids as the basic photo-protectants, which overcomes the drawbacks of the methods known in the art and which provides compensatory increased levels of photo-protectants and antioxidants in the body when most needed, because they are quickly consumed or otherwise their concentration in the system decreases at a high rate, thus affording a systemic protective action.

The invention is therefore directed to a soft drink which contains a carotenoid mix, alone or together with vitamin C and/or vitamin E and/or other antioxidants, in an amount which does not exceed 10 Vitamin A RDA (Recommended Daily Allowance) equivalents of pro-Vitamin A carotenoids per liter of cool drink. Thus, intake of carotenoids and related photo-protectants is a function of exposure to sun and heat. The more exposed is the subject to the sun, the greater the amount of carotenoids that he will consume, because thirst and drinking responses are evoked proportionally to the extent/level of exposure to sun and heat.

It should be understood that the addition of Vitamins C and E or selenium to the carotenoids-containing drink has a synergistic effect, inasmuch as reduced glutathione (GSH) and Vitamin E are involved in the prevention of peroxidation of nuclear material, and Vitamin C, through its regenerating effect on Vitamin E is also active in this fashion. Thus, these additives can contribute protection in the initiation phase of skin damage, whereas carotenoids are rather effective in the later promotion stages of the photo-process.

Additional useful additives comprise antioxidants and factors directly or indirectly related to radical scavengers, such as GSH or Se, and CoQ10. These may be added as isolated materials or as naturally occurring components of vegetable/fruit juices and/or herbal preparations.

Normally a carotenoids mix will contain a number of carotenoids, such as β-carotene, canthaxanthin, zeaxanthin, lycopen, lutein, crocetin, capsanthin, etc. The RDA equivalent of such a mix will be calculated based on the relative pro-Vitamin A activity of the carotenoids which do have pro-vitamin activity, e.g., β: 100%, α: 50–54%, γ: 42–50%, β-zeacarotene: 20–40%, cryptoxanthin: 50–60%, β-apo-8'-carotenal: 72%, β-apo-12'-carotenal: 120%, etc., assuming that ail the carotenoids with provitamin activity will be converted into Vitamin A.

Among the various advantages of the invention, it should be mentioned also that a drink is an excellent vehicle for the purposes of the invention, because it is generally accepted and proven that drinking in warm weather is beneficial. Furthermore, thirst can be induced by the addition of sugars or equivalent materials in relatively high proportions, to stimulate further drinking. Stimulation of the will to drink the mix according to the invention will be better achieved, of course, with tasty drinks.

Using the drink of the invention as the application method, the danger of overdosage becomes minimized, because overdosage may occur whenever a too-high amount of material is absorbed, which is not subsequently utilized by the body because it is not highly needed by the body as when exposed to sun in a manner that will prime the body to consume the photo-protectants. With the proportional intake of material through the drink according to the invention, this problem is inherently resolved.

It has further been found that Vitamin C protects carotenoids and, therefore, the addition of Vitamin C permits to operate with lower carotene concentrations, which is of course desirable. Furthermore, synergism between Vitamin C and Vitamin E exists, inasmuch as Vitamin E (tocopherol) is regenerated from tocopheryl radical by Vitamin C.

Vitamin C can also be supplied in other forms or precursors which can be metabolised to obtain Vitamin C, such as ascorbyl palmitate. Ascorbyl palmitate itself was found more effectively protecting carotene and internal organs, e.g., liver, against free radicals, when compared to ascorbic acid. This might be because it is easier to dissolve in fatty tissues.

While the limiting amount of pro-Vitamin A carotenoids and vitamins to be taken daily are of course the updated RDA, some examples of increased concentrations and other compositions to be used according to the invention will be detailed hereinafter. It is of course understood that the following examples are provided only for the purpose of illustration, and have no limiting purpose. Various flavors and additives detailed hereinafter are also detailed only by way of example, and a person skilled in the art will be able to provide additives, flavors and the like which match the drink which it is desired to provide.

Among the many additives which can be employed, tonic herbs are possible convenient additives, including, e.g., Borrage, Aloe-Vera, Peppermint, Lemon, Ginseng, Barley-water, Anise, Grapes, Raspberries, Strawberries, Hawthorn berries, Rosemary, Watercress, Guarana, Papavera Rhoea, Achilea Milfolia, Arcitium Lappaa, Chrysanthemum, Parthenium, Cola vera, Elentherococcus, Bingo Bilboa, Japanese apricot (UMA) etc.

The following examples of compositions will illustrate some of the many possible uses of the invention. While some examples of active material contents are specified hereinafter, the man of the art will appreciate that many different combinations of carotenoids and other active ingredients can be provided, depending on the requirements from the final composition concerning flavor, color, RDA, etc.

In general, addition of active materials can be done, e.g., by following the general directions given below.

Milk/Fat Soluble Liquids

Fat emulsion carotenoid mix: β-carotene 30% suspension: 8 mg (for light drinks, e.g., Pina Colada) up to 25 mg (butter raspberry), 60 mg (cocoa), for each liter of cocoa/raspberry butter milk preparation. Apocarotenal (yellow-orange brown color), 30% fat emulsion base: 5–15 mg/liter for cocoa, and other coffee-based liquids and ices. Canthaxanthin 1% water soluble: 500–2000 mg/liter in strawberries and cocoa preparations. α-tocopherol (e.g., Hoffmann-La Roche): 0–400 mg/liter drink.

Water-Based Drinks

Carotenoid mix such as canthaxanthin 10% (water soluble) powder and β-carotene 1% powder. Dark drinks such as raspberries, strawberries or cola will contain (for each liter) the following: 350–2500 mg β-carotene 1%. and 500–1500 mg canthaxanthin 10%. Apo-carotene 30% fat emulsifier base, 1:1 mixed with emulsifier for ginger ale: 5–15 mg/liter.

For light colored drinks, mostly β-carotene, e.g., 350 mg/liter for lemon drink and 700–2500 mg/liter for mint drinks.

Vitamin C: water soluble mix: L-ascorbic acid or ascorbate salts, according to taste considerations, between 50–2000 mg/liter. Ascorbyl palmitate (water insoluble) mix: 1:1 ratio or ascorbyl palmitate and emulsifier: range of use: 200–8000 mg mix/liter drink.

EXAMPLE 1

Instant Mandarin-Orange Powder

A powder to be dissolved in water (130 g/liter) is prepared by admixing the following ingredients: 82.73% sucrose/white sugar, 10% flavorings (such as HNR flavor mandarin-orange 48230), 3% citric acid, 3% dextrose, 1% cloudifier (e.g., HNR). Buffers: 0.5% tri-sodium citrate, 0.5% tri-calcium phosphate. 0.2% ascorbic acid, 0.07% food color.

Diet version: Based on a sweetness index of sucrose=1, 1/200 parts of Aspartane or 1/250 parts of Acesulfame-K are substituted for each part of sugar.

To the above there are added 1–5 RDA equivalents of β-carotene and α-tocopherol in water base emulsion and L-ascorbic acid (Hoffmann-La Roche) or ascorbyl palmitate (ICN Biochemicals).

EXAMPLE2

Orange Drink

An orange drink can be prepared containing 150 g juice (10.5 BX) or 24.6 orange coneentrate 64 BX, 89.25 g sucrose, 2.77 g lemon acid, flavors, stabilizers, buffer citrate (to prevent tartar) and extracts, 883.38 g water, carotenoids mix: 8 mg %, Vitamin C equivalent: 20 mg %.

The composition of the invention can also be provided in a milk/fat-water emulsion. The following are examples of such compositions.

EXAMPLE 3

Instant Chocolate Beverage

A formulation (8–10%/liter milk) will contain 67% sucrose/sugar, 30% cocoa powder, 1% lecithine and 2% satia gum, carotenoid mix, 6 mg %, Vitamin E, E.E. (α-tocopherol equivalent) 6 mg %, coenzyme Q10.

EXAMPLE4

Vegetarian Milk Base: Pinacolada

The drink will contain 5% coconut oil, 0.1% emulsifiers, 8–10% sugar, 0.1% pinacolada flavor, and active ingredients as in the previous examples.

EXAMPLE 5

Ice Cream

An ice cream may contain about 10% of fat, 12% fat-free milk solids, 15% sugar, 3% corn syrup, color extracts and flavors, and active ingredients as in the previous examples.

EXAMPLE 6

Raspberry Ice Butter-milk

Butter-milk 61.45%, raspberry pulp 15.5%, sucrose 14%, corn syrup 6%, butter 3%, emulsifier (lecithine) 0.2%, stabilizers e.g., Lygomme ELB 0.2% (pH 3.8–4.0), active ingredients as in the previous examples.

EXAMPLE 7

Camomille Summer Punch (Tonic)

A strong infusion (concentrated hot-water herbal extract with or without ½ ethanol) with pineapple, papaya and honey. Add mint and strawberry cubes for color and taste. Active ingredients as defined above.

EXAMPLE 8

Herbal (Mint) Drops

A strong infusion: 4–8 teaspoons peppermint in 1 cup boiling water, steeping the infusion in a covered container for a few hours, refrigerated. 50 Drops added to lemonade drink. Active ingredients as defined above.

EXAMPLE9

Teas

Rose Hip Tea Blend (cold Vitamin C drink):

1 cup dried rose hips, 1 3-inch stich cinnamon, ¼ cup dried lemon balm leaves, 1 teaspoon dried grated organic lemon rind.

Rose Hip and Blackberry Cordial:

2 tcabags rose hips (Pompadour brand), 1–2 teaspoons blackberry cordial, 1 cup boiling water. Steep together and serve.

Peppermint-Alfalfa Tea Blend:

1 cup peppermint or spearmint or bee balm leaves, 1 cup dried alfalfa leavcs.

Active materials as defined above.

EXAMPLE 10

Lemon Mint Blend

Water Preparation

½ cup dried peppermint leaves, 1 cup dried alfalfa leaves, 3 tablespoons dried lemon balm leaves, 3 tablespoons dried, grated lemon rind. Solids: 1 teaspoon (250 g sucrose/liter). Active ingredients as defined above.

EXAMPLE 11

Compound Barley Water

2 pints simple barley water (4 ounces barley, whole, 2 ounces honey, lemon peel washed of ½ lemon: Add 1 pint of water to barley and lemon peel. Simmer until soft. Remove from heat. Steep. Add honey.), 1 pint hot water, 2½ ounces sliced figs, ½ ounce, sliced and bruised licorice root, 2½ ounces raisins. Boil down to 2 pints. Strain.

EXAMPLE 12

Ginger Ale

1 large piece ginger root, bruised, 1 pint boiling water, 1 tablespoon honey, Perrier water as needed. Boil water, add bruised ginger root and simmer for fifteen to twenty minutes. Strain out root. Add honey and mix well. Combine with Perrier water. Don't use powdered ginger.

EXAMPLE 13

Drink Powder

"Orange Taste"

(values expressed as percentage/content in the end user preparation): 10% sugar, 1% carotene mix. (Diet should be 1/200 aspartame or 1/250 acesulfam.) 0.1% citric acid. 0.9% tasters. 0.1–0.2% stabilizers (CMC, guargum, etc.). Buffer—Na_3 citrate extracts.

As will be apparent from the above examples, preparing a mixcd carotenoids drink according to the invention is simple and economic. It should be understood, as detailed above, that the word "drink" throughout this specification is meant to include also frozen or semi-frozen liquids, such as ice cream and sorbets.

EXAMPLE 14

Fruit Ice Strawberry Sorbet

Sucrose 21.5%, corn syrup (DE 36–38) 6.5%, strawberry puree 24.15%, strawberry concentrate 2.5%, satia algin GAX-900 0.35%. pH 3.3–3.5, water 45%.

Weed juice and pineapple: mint, alfalfa, filaree, dandelion, romaine leaves, parsley, celery tops, carrot tops, 2 cups pineapple: Combine handfuls and extract into juice. Place handfuls of these weeds and home greens in the juice extractor, use 1 cup to each 2 cups of pineapple. This green juice may be made into ice cubes and used.

Nutritional and RDA data for the components of the drink of the invention are well known to persons skilled in the art, and change from time to time. Illustrative data are reported below, based on values accepted at the time of filing of this application:

RDA was formerly defined in terms of International Units, I.U., defined as 0.3 μg of crystalline ail-trams retinol, or 0.6 μg β-carotene. Since 1980, RDA for Vitamin A is commonly stated in μg and R.E. For the adult male, the RDA is set at 1000 RE (750 as retinol and 250 as β-carotene, 5000 I.U.), while the RDA for women is lower, at 800 RE (4000 I.U.). Children need 400 to 1000 RE (2000 to 5000 I.U.), increasing from infancy to 14 years. The amount of β-carotene required for 1 RE is 6 μg, while the amount required for other provitamin A carotenoids is 12 μg. 1 RDA carotene is the provitamin A equivalent of 5000 1.U. Vitamin A.

I claim:

1. A synergistic food-stuff composition concentrate consisting essentially of

(A) one or more edible carotenoids selected from the group consisting of α, β and γ carotenes, zeaxanthin, lycopen, lutein, crocetin, capsanthin, β-zeacarotene, cryptoxanthin, β-apo-8'-carotenal and β-apo-12'-carotenal;

(B) water;

(C)(1) at least one physiologically-acceptable antioxidant selected from the group consisting of ascorbic acid and salts thereof, and tocopherols; or

(2) at least one physiologically-acceptable free-radical scavenger selected from the group consisting of reduced glutathione and coenzyme Q10; or

(3) at least one physiologically-acceptable antioxidant selected from the group consisting of ascorbic acid and salts thereof, and tocopherols, and at least one physiologically-acceptable free-radical scavenger selected from the group consisting of reduced glutathione and coenzyme Q10.

2. A food-stuff composition for oral consumption comprising an effective amount of the concentrate according to claim 1 for systemic protection against the harmful effects of solar radiation, wherein the concentration of component (A) of the concentrate in said food-stuff composition does not exceed 10 times the U.S. recommended daily allowance for provitamin A active carotenoids per liter.

3. A method for protecting against the harmful effects of exposure to solar radiation, comprising orally administering to a person in need of such protection during exposure to solar radiation a prophylactic effective amount of a synergistic food-stuff composition comprising:

(A) at least one edible carotenoid selected from the group consisting of α, β and γ carotenes, zeaxanthin, lycopen, lutein, crocetin, capsanthin, β-zeacarotene, cryptoxanthin, β-apo-8'-carotenal and β-apo-12'-carotenal;

(B) water;

(C) (1) at least one physiologically-acceptable antioxidant selected from the group consisting of ascorbic acid and salts thereof, and tocopherols; or

(2) at least one physiologically-acceptable free-radical scavenger selected from the group consisting of reduced glutathione and coenzyme Q10; or

(3) at least one physiologically-acceptable antioxidant selected from the group consisting of ascorbic acid and salts thereof, and tocopherols, and at least one physiologically-acceptable free-radical scavenger selected from the group consisting of reduced glutathione and coenzyme Q10;

wherein when the composition is administered the amount of carotenoids does not exceed 10 times the U.S. recommended daily allowance for provitamin A active carotenoids per liter.

4. The composition of claim **2**, further comprising a flavoring selected from the group consisting of borrage, aloe-vera, peppermint, lemon, ginseng, barley-water, anise, grapes, raspberries, strawberries, hawthorn berries, rosemary watercress, guarana, papavera rhoea, achillea milfolia, arcitium lappa, chrysanthemum, cola vera, eleutherococcus, ginkgo biloba and japanese apricot.

5. The composition of claim **2**, wherein the antioxidant is ascorbic acid or a sait thereof.

6. The composition of claim **2** wherein the antioxidant is a tocopherol.

7. The composition of claim **1**, wherein the antioxidant is an alpha tocopherol.

8. The composition of claim **2**, wherein the composition is in an emulsified base.

9. The composition of claim **2**, wherein the composition is in a milk base.

10. The composition of claim **2**, wherein the composition is in a concentrated form.

11. The composition of claim **2**, wherein the composition is in a drinkable form.

12. The composition of claim **2**, wherein the composition is in a semi-frozen form.

13. The composition of claim **2**, wherein the composition is in a frozen form.

* * * * *

Fiche conseil AZ

Huile végétale de Pépins de Tomate

32 avis

Riche en antioxydants puissants dont le lycopène, les caroténoïdes, les phytostérols et les tocophérols, cette huile possède des propriétés anti-âge hors norme. Rare et précieuse, elle s'incorpore dans vos préparations de soins bonne-mine et pour peaux matures et agressées.

-- Contenance --
Quantité :
1
+ -
2,50 €

Présentation

Carte d'identité

Procédé d'obtention

Première pression à froid

Partie de la plante extraite
Graines
Nom botanique
Solanum lycopersicum
Famille botanique
Solanacées
Fonction
Ingrédient cosmétique
Qualité

100% pure et naturelle, **vierge**, première pression à froid sans aucun traitement chimique

Pays d'origine
Chine (lot QHV0209) et Europe (lot SHV0074)
Culture

Ecologique (lot QHV0209) et Conventionnelle (lot SHV0074)

Culture conventionnelle

Potentiel oxydatif
En savoir plus sur le potentiel oxydatif des beurres et huiles...
Consignes de tri de l'emballage

Téléchargez les consignes de tri de nos emballages

Qualité

Date de production
Juin 2015 (lot QHV0209) et Mai 2017 (lot SHV0074)
A utiliser de préférence avant fin
Juin 2018 (lot QHV0209) et Mai 2019 (lot SHV0074)

Sur l'étiquette, le numéro de lot est suivi d'une lettre indiquant la série de conditionnement.

Propriétés organoleptiques

- Aspect : liquide huileux fluide
- Couleur : rouge-orangé
- Odeur : végétale, caractéristique, légèrement épicée, évoquant les tiges de tomate
- Toucher : pénètrant
- Saveur : caractéristique

Densité
0.91-0.93
Indice de saponification
184-195
Composition

Composition en acides gras Chromatographie phase gaz du lot QHV0209 :

- Acides gras essentiels poly-insaturés (AGPI ou AGE) ou vitamine F : **acide linoléique (oméga-6) (47.83%)**
- Acides gras mono-insaturés (AGMI) : **acide oléique (oméga-9) (24.80%)**
- Acides gras saturés (AGS) : acide palmitique (13.31%)

Composition en acides gras Chromatographie phase gaz du lot SHV0074 :

- Acides gras essentiels poly-insaturés (AGPI ou AGE) ou vitamine F : **acide linoléique (oméga-6) (47.73%)**
- Acides gras mono-insaturés (AGMI) : **acide oléique (oméga-9) (21.13%)**
- Acides gras saturés (AGS) : acide palmitique (13.63%)

Zoom sur l'acide linoléique : *l'acide linoléique est un acide gras polyinsaturé appartenant à la famille des oméga-6. Cet acide gras n'est pas synthétisé par l'organisme. On dit pour cela que c'est un acide gras "essentiel". Une carence en oméga-6 peut entraîner une sécheresse intense de la peau et des allergies. Au niveau cutané, cet acide gras entre dans la composition des céramides. Il participe à la reconstitution des lipides épidermiques et favorise la bonne cohésion des cellules de la peau entre elles. L'acide linoléique permet de limiter les pertes en eau de la peau tout en présentant des qualités adoucissantes et nutritives.*

<u>Autres constituants actifs</u> :

- **Insaponifiables dont :**
- **Stérols (4253 mg/Kg) dont béta-sitostérol (50.5 %)**, cholestérol (18.6%), stigmastérol (10.7%), Δ5-avénastérol (7.9%), campestérol (4.3%), Δ7-cholestérol (2.3%)
- **Vitamine E : tocophérols (1029.7 mg/Kg)** dont gama-tocophérol (991.1 mg/Kg), alpha-tocophérol (34.0 mg/Kg), delta-tocophérol (3.2 mg/Kg et béta-tocophérol (1.4 mg/Kg)
- **Eléments minéraux :** Potassium, Magnésium, Phosphore, Sodium, Calcium, et dans une moindre mesure Manganèse, Fer, Zinc et Cuivre
- **Composés phénoliques (quercétine, kaempférol, myricétine...)**
- **Caroténoïdes** et **xanthophylles** (lycopène, lutéine, zéaxanthine...) dont 30.8 mg/kg de **lycopène**

Conditions de conservation
Huile végétale assez sensible à l'oxydation. Se conserve de préférence dans un endroit frais (éventuellement au réfrigérateur), dans son emballage d'origine, fermé, à l'abri de l'air et de la lumière.

Propriétés et utilisations

Propriétés

- **Exceptionnellement riche en antioxydants**, notamment lycopène et autres caroténoïdes, c'est un actif de choix pour les soins anti-âge.
- Effet "bonne-mine", elle **ravive le teint**.
- Grâce à sa teneur en antioxydants, elle lutte contre le photovieillissement et les dommages liés aux radicaux libres.
- Elle **affine** et **tonifie** le grain de peau.
- Excellent émollient, elle **assouplit** la peau et aide à maintenir son hydratation.

Indications

- Peaux exposées au stress oxydatif (pollution, tabac, stress...)
- Vieillissement cutané
- Peaux sujettes à inconfort
- Peaux matures
- Peaux sèches
- Peaux mixtes à grasses

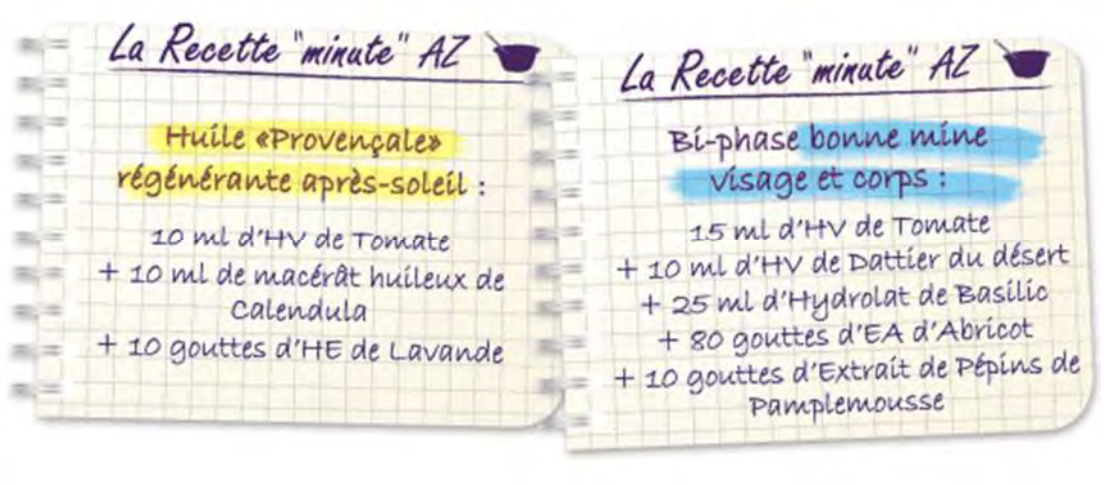
Utilisations

S'utilise en tant qu'ingrédient dans vos préparations de soins pour la peau :

- Soins bonne-mine
- Préparation au soleil, soins après-soleil
- Soins anti-âge et anti-rides
- Maquillage

Quelques idées

- Sérum rides et ridules
- Soin préparateur de bronzage
- Baume à lèvres jeunesse
- Lait après soleil
- Huile réparatrice, revitalisante



Synergies

- **Pour lutter contre les radicaux libres** : huiles végétales de Buriti, de Framboise, et de Cranberry, Urucum, Coenzyme Q10, ...
- **Pour son effet "bonne-mine" et prolongateur de bronzage** : huile végétale de Chaulmoogra, macérât huileux de Carotte, extrait de Carotte, actif cosmétique DHA, ...
- **Pour une action anti-âge** : huiles végétales de Rose musquée, Cranberry, Framboise et Bourrache, huiles essentielles de Bois de Rose et Curcuma, actifs cosmétiques Algo'boost Jeunesse, AHA acides de fruits, ...

En pratique

- L'huile végétale de Pépins de tomate s'utilise en tant qu'ingrédient dans vos préparations cosmétiques.
- De par sa coloration orangée prononcée, nous conseillons de l'utiliser diluée à hauteur de 1 à 30%, en mélange dans votre préparation huileuse.
- S'utilise en tant que phase grasse dans la composition de crèmes pour le corps et le visage.
- En raison des éventuels risques d'oxydation liés à la sensibilité de cette huile végétale, nous vous recommandons d'ajouter de la vitamine E ou de l'extrait CO2 de Romarin avant chauffage pour incorporation dans une émulsion, ou bien de l'introduire à froid.

Propriétés

- Donne **éclat** et **lumière** aux **cheveux colorés** ou méchés.
- **Prolongeant** la **couleur** ou les mèches, elle réduit notamment l'impact des UV.
- Riche en **antioxydants**, intéressante pour **protéger la chevelure** des effets des radicaux libres (soleil, pollution, tabac...)
- **Nourrit** et **hydrate** les cheveux.

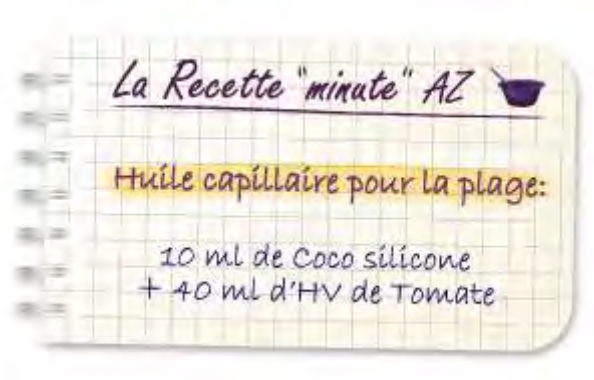
Indications

- Cheveux colorés ou méchés
- Cheveux dévitalisés, fragiles, abîmés

Utilisations

S'utilise en tant qu'ingrédient dans vos préparations de soins pour les cheveux :

- Sérums et masques capillaires protection couleur
- Soins capillaires avant et après-soleil
- Après-shampooings et baumes capillaires démêlants, régénérants
- Baumes capillaires nourrissants et protecteurs



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Découvrez notre fiche savoir-faire " **Soin du visage** " pour en apprendre davantage et construire votre programme personnalisé...

Découvrez notre dossier thématique " **Le Cheveu** " pour en apprendre davantage et construire votre programme de soin capillaire personnalisé...

En savoir +

La Tomate appartient à la famille des **Solanacées**. Bien connue de tous, elle se caractérise par sa **couleur rouge vif**, qu'elle doit à sa **richesse en caroténoïdes** et notamment en **lycopène**, puissant antioxydant. On extrait des graines de ce fruit-légume une huile à la **magnifique couleur rouge-orangée** et particulièrement riche en antioxydants dont le lycopène. Il s'attaque aux radicaux libres responsables du **vieillissement prématuré** de l'organisme et de la peau.

Sa forte teneur en vitamine E (tocophérol) renforce son **action antioxydante** et en fait une huile nourrissante et protectrice.
Pour finir, les nombreux minéraux qu'elle contient assurent une **bonne teneur en eau dans l'épiderme** et stimulent la synthèse de collagène, assurant une **bonne élasticité** de la peau.
Cette huile riche en nutriments et en ingrédients bioactifs ravivera et redonnera éclat à votre peau et vos cheveux.

***AVERTISSEMENT** : Ces propriétés, indications et modes d'utilisation sont tirés des ouvrages ou sites Internet de référence en aromathérapie, hydrolathérapie et phytothérapie. On les y retrouve de façon régulière et pour beaucoup confirmés par des observations en milieu scientifique. Toutefois, ces informations sont données à titre informatif, elles ne sauraient en aucun cas constituer une information médicale, ni engager notre responsabilité. Pour tout usage dans un but thérapeutique, consultez un médecin.*

Réponse d'un candidat

Note attribuée à cette copie 13 / 20

PARTIE INTRODUCTIVE

La présente invention appartient au domaine des compositions à base d'extraits végétaux.

La présente invention porte particulièrement sur des compléments alimentaires à base de caroténoïdes permettant la coloration de la peau et la prévention de brulures causées par le soleil.

La chaleur de la peau et son intensité dépendent de plusieurs facteurs, dont le contenu de kératinocytes en mélanine, du type de mélanine présent dans lesdits kératinocytes, de la vitesse de desquamation etc…

Essentiellement pour des raisons esthétiques, en Occident, l'homme s'expose de plus en plus au soleil, pour avoir une peau bronzée. Or les radiations ultraviolettes (UVA et UVB), qu'elles proviennent des rayonnements du soleil ou de lampes à bronzer, présentent des dangers pour la santé et entraînent un vieillissement prématuré de la peau.

C'est pourquoi, les consommateurs sont de plus en plus intéressés par des produits qui procurent à la peau une coloration proche de celle d'un bronzage naturel sans pour autant qu'il soit nécessaire de s'exposer à des rayonnements ultraviolets.

Il serait donc extrêmement avantageux de pouvoir trouver une moyen permettant d'induire un bronzage sans impliquer en s'affranchissant les dangers liés aux rayonnements UVA et UVB. Il serait encore plus avantageux que ces moyens soient naturels.

Il *ressort de diverses études publiées ces dernières années que la caroténoïdes présentent la propriété d'induire la synthèse de mélanine*.

Le document GB2222222 divulgue une composition comprenant des carotènes et du lycopène afin d'augmenter le taux sanguin de caroténoïdes pour prévenir les cancers.

Le document US20000 divulgue lui des compositions à boire comprenant des caroténoïdes particulièrement des carotènes pour la protection contre les effets de la lumière UV.

Le document « D3 » divulgue les bienfaits des extraits de pépins de tomate dont leur teneur en caroténoïdes.

NB : le texte en italique est un extrait collé du sujet

Les présents inventeurs sont parvenus à formuler une composition permettant à la fois d'augmenter la coloration de la peau mais également de prévenir l'érythème lié à une exposition au soleil. Cette composition peut en outre être formulée à partir d'extraits végétaux. Un premier objet de l'invention est donc une composition telle que décrite selon la revendication 1.

Cette composition peut être utilisée afin de prévenir les érythèmes liés à une exposition au soleil.

Un autre objet de l'invention est donc décrit à la revendication 10. D'autres objets sont définis selon les revendications dépendantes.

REVENDICATIONS

1 Composition comprenant un mélange de caroténoïdes, ledit mélange de caroténoïdes comprenant :
- du lycopène, et
- un ou plusieurs carotènes, choisis parmi l'alpha carotène et le beta carotène

caractérisée en ce que le ratio entre la teneur en poids total en carotènes de la composition et la teneur en lycopène de la composition est inférieur ou égal à 1.

2 Composition selon la revendication 1, caractérisée en ce que le mélange de caroténoïdes comprend en outre de la lutéine.

3 Composition selon la revendication 1 ou 2, caractérisée en ce que le mélange en caroténoïdes comprend en outre de la zéaxanthine et/ou de la cryptoxanthine.

4 Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que la caroténoïdes sont issus d'extraits de fruits et/ou légumes.

5 Composition selon la revendication 4, caractérisée en ce que les caroténoïdes sont issus d'extraits de carotte ou d'extraits de pépin de tomate.

6 Composition selon l'une quelconque des revendications 1 à 5, ladite composition étant contenue dans une capsule semi solide apte à être ingérée.

6 Composition selon l'une quelconque des revendications 1 à 5, comprenant en outre au moins un excipient adapté à une administration par voie orale choisi parmi les huiles végétales neutres, l'huile de blé, l'huile de pépin de raison, l'huile de tournesol et l'huile de sésame.

7 Composition selon l'une quelconque des revendications 1 à 6, ladite composition comprenant en outre des vitamines et/ou oligoéléments.

8 Composition selon la revendication 7, dans laquelle les vitamines sont choisies parmi la vitamine B5, la vitamine C, la vitamine D et la vitamine E.

9 Procédé pour la préparation de la composition selon l'une des revendications 1 à 8, ledit procédé comprenait une étape d'extraction de caroténoïdes à partir d'extraits de fruits et/ou légumes.

10 Composition selon l'une quelconque des revendications 1 à 8, pour son utilisation dans le traitement et/ou la prévention de l'érythème solaire.

11 Composition pour son utilisation selon la revendication 10, dans laquelle composition est pour administration par voie orale.

12 Composition pour son utilisation selon la revendication 11, caractérisée en ce que ladite composition est administrée une ou deux fois par jour et la teneur en carotène de la composition est comprise entre 0,5 et 3 mg.

LETTRE AU CLIENT

Cher Monsieur BEAUREGARD,

Veuillez trouver ci-joint le projet de jeu de revendications et de partie introductive pour votre demande de brevet.

Nous avons noté que vous avez développé une plaquette publicitaire décrivant le contenu de votre composition 1. Nous notons la date de juillet 2018 sur cette plaquette et en concluons donc que cette plaquette n'a pas été diffusée au public. Merci de nous confirmer ce point. Il faudra déposer la demande avant sa diffusion.

Nous avons également noté que vous avez déjà utilisé des extraits de fruits pour d'autres applications, nous assumons que ces extraits n'étaient pas formulés sous forme des compositions exemplifiées.

Au vu des données expérimentales fournies, nous avons éliminé les compositions associées à un érythème solaire. Il en ressort que toutes les compositions permettant une coloration de la peau et la prévention de l'érythème ont pour point commun d'avoir un ratio carotène/lycopène inférieur ou égal à 1. Nous vous proposons donc d'utiliser cette caractéristique dans la composition revendiquée.

Les documents que vous nous avez fournis ne divulguent pas ce ratio spécifique.

D1 divulgue des compositions comprenant nécessairement plus de carotènes que de lucopènes (et donc un ratio carotène/lycopène supérieur à 1).

D2 divulgue des compositions sans spécifiquement y ajouter du lycopène (le lycopène est juste mentionné comme étant un caroténoïde).

D3 divulgue les bienfaits des caroténoïdes extraits de pépins de tomate, indique que la combinaison de tels extraits à des extraits de carotte peut permettre d'apporter des bienfaits en terme de bronzage mais ne divulgue pas le ratio mentionné ci-dessus.

Nous avons noté qu'un des atouts de vos compositions est qu'elles soient faites avec des extraits naturels. Cependant, vous indiquez que vos données ont été obtenues avec des extraits synthétiques. Nous n'avons donc pas introduit cet aspect « essentiel » d'extrait naturel dans la revendication 1.

Toutes vos compositions incluent lutéine mais est-ce essentiel ? Avez-vous des comparatifs sans lutéine ? Si essentiel : nous introduirons la revendication 2 dans 1.

Vos compositions ont un effet thérapeutique : revendication composition pour utilisation traitement maladie (ici érythème solaire) : effet thérapeutique indissociable du cosmétique.

Vous indiquez un effet de coloration obtenue avec composition 3 et 5 en application sur la peau. Il s'agit d'une utilisation cosmétique qui peut être protégée sous la forme d'une revendication « d'utilisation cosmétique de la composition pour la coloration de la peau, ladite composition était appliquée typiquement sur la peau ».

Cette application ne « fonctionnait pas avec les autres compositions que la 3 et la 5, et la composition 3 n'était pas couverte par la revendication 1 (car elle entraînait un érythème solaire) il faudrait couvrir cette application avec une autre demande. Il faudrait idéalement déposer cette demande le même jour que la présente demande.

Concernant le changement de législation : les brevets ne sont pas tenus de s'y tenir dans revendications. Il faudra que vous fassiez à cet aspect seulement lors de la production et commercialisation des compositions. Nous n'avons donc pas à préciser que le carotène est administré à 3mg/jour maximum.

Vous indiquez ne pas souhaiter divulguer votre procédé secret pour plus de 18 mois ? Sinon nous pouvons, s'il est pour l'instant nouveau essayer de l'intégrer car la demande ne sera publiée que dans 18 mois.

Enfin nous avons rédigé 12 revendications. Chaque revendication au-delà de la 10ème entraîne une taxe de 42 € (21 € si petite entité). Nous pouvons réduire les revendications à 10 si vous ne souhaitez pas payer de taxe de revendication supplémentaire.

RAPPORT DES EXAMINATEURS

EPREUVE ECRITE N° 1

REMARQUES GENERALES SUR LA PREMIERE EPREUVE ECRITE

Il apparaît très nettement que les candidats qui ont proposé les meilleures revendications sont ceux qui ont fourni un effort de compréhension et d'analyse technique de l'invention et de l'art antérieur.

Concernant la portée des revendications, il semble utile de rappeler que les revendications doivent répondre à toutes les conditions de brevetabilité et notamment à l'exigence de nouveauté ET d'activité inventive. La recherche d'une protection la plus large possible ne doit en effet pas conduire à la position extrême consistant en une absence totale de protection pour défaut de nouveauté ou d'activité inventive des revendications principales.

Il semble également utile de rappeler que tous les aspects de l'invention doivent être protégés et notamment qu'il est important de bien penser à toutes les catégories de revendications envisageables. En cas de défaut d'unité d'invention, ces éléments doivent être mentionnés dans la lettre au Client.

ANALYSE DU SUJET

La société Biopure a mis au point un complément alimentaire à activité bronzante à base notamment de caroténoïdes.

Les compléments alimentaires 1 à 16 dont la composition est donnée dans le tableau 1, comprennent une base de formulation, de l'alpha carotène, du béta carotène, éventuellement d'autres caroténoïdes tels que du lycopène, etc…

Le tableau 1 donne pour chaque complément, le rapport carotènes (alpha et/ou beta)/lycopène.

Le tableau 2 montre que tous les compléments testés ont une activité bronzante lorsqu'ils sont administrés par voie orale.

L'histogramme donne pour chaque complément alimentaire testé, l'évaluation de l'érythème solaire observé après exposition au soleil.

En ce qui concerne l'art antérieur :

Analyse de D1 :

D1 décrit des compléments alimentaires à base de caroténoïdes, notamment riches en alpha carotène, beta carotène et lycopène.

En particulier sont décrits des compléments alimentaires comprenant de 20-40 % d'alpha carotène, de 55-80 % de beta carotène et de 3-20 % de lycopène.

Ces compléments alimentaires sont destinés à compenser un défaut d'apports naturels en caroténoïdes. Aucune activité bronzante découlant de l'ingestion de ces compléments alimentaires n'est décrite dans D1.

Analyse de D2 :

D2 décrit une boisson comprenant un mélange de caroténoïdes en tant que composés photo-protecteurs, éventuellement en association avec d'autres composants tels que de la vitamine C et/ou E et/ou d'autres anti-oxydants.

Le mélange de caroténoïdes peut comprendre un certain nombre de caroténoïdes tels que du beta carotène, du lycopène et d'autres caroténoïdes.

D2 ne divulgue pas l'activité bronzante des caroténoïdes.

Analyse de D3 :

D3 est un document divulguant que l'huile végétale de pépins de tomate renferme entre autres composants, des caroténoïdes et des xanthophylles (lycopène, lutéine, zéaxanthine, …).

D3 indique également que l'huile de pépin de tomate peut être utilisée en tant qu'ingrédients dans des compositions à application topique pour raviver le teint et préparer la peau au bronzage.

D3 ne divulgue pas de complément alimentaire à base d'huile de pépins de tomate.

Nouveauté

Il ressort de D1 et D2 que des compléments alimentaires comprenant des carotènes (alpha et/ou beta) et du lycopène sont déjà connus.

Par contre, l'activité bronzante de ces compléments alimentaires n'est pas divulguée dans D1 et D2.

Cependant, selon les indications mentionnées dans la lettre du client, il est connu que les caroténoïdes présentent la propriété d'induire la synthèse de mélanine et que de ce fait, lorsqu'ils sont ingérés par voie orale, ils permettent de conférer à la peau une coloration proche de celle d'un bronzage naturel.

Aucun des documents analysés ne décrit un complément alimentaire comprenant un ratio particulier carotènes/lycopène.

Activité inventive

Il ressort des résultats présentés dans l'histogramme de la page 8 du sujet, que seuls certains compléments alimentaires comprenant un ratio particulier carotènes/lycopène ont un effet sur la protection de l'érythème solaire après exposition au soleil. Il s'agit des compléments alimentaires n°1, 5, 7, 8, 12, 13, 15 et 16.

Ces compléments alimentaires présentent tous un ratio carotènes/lycopène compris entre 1/1 et 1/10.

L'effet technique correspondant est l'obtention d'un complément alimentaire présentant à la fois une activité bronzante (coloration de la peau sans soleil) et de protection de la peau contre l'érythème solaire.

Ces proportions particulières n'étant ni divulguées, ni suggérées par l'art antérieur, une revendication principale de complément alimentaire reprenant cette caractéristique a été jugée conforme aux exigences de nouveauté et d'activité inventive.

EXEMPLE DE REVENDICATIONS ATTENDUES

1. Composition comprenant des caroténoïdes, comprenant :

- au moins un carotène choisi parmi l'alpha-carotène, le beta-carotène et leurs mélanges,
- au moins du lycopène,

caractérisée en ce que le rapport massique carotène/lycopène varie de 1/1 à 1/10.

2. Composition selon la revendication 1, caractérisée en ce que la quantité de lycopène est de 2 à 25 mg.

3. Composition selon la revendication 1 ou 2, caractérisée en ce que la quantité totale de carotène est de 0,5 à 3 mg.

4. Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce qu'elle comprend en outre au moins une xanthophylle choisie parmi la zéaxanthine, la lutéine, la cryptoxanthine et leurs mélanges.

5. Composition selon l'une quelconque des revendications 1 à 4, caractérisée en ce que les caroténoïdes sont extraits de fruits ou de légumes.

6. Composition selon l'une quelconque des revendications 1 à 4, caractérisée en ce qu'elle se présente sous la forme de capsules.

7. Composition selon l'une quelconque des revendications 1 à 6, caractérisée en ce qu'elle comprend des huiles végétales neutres choisies dans le groupe comprenant l'huile de soja hydrogénée, l'huile de blé, l'huile de pépin de raisin, l'huile de tournesol, l'huile de sésame, et leurs mélanges.

8. Composition selon l'une quelconque des revendications 1 à 6, caractérisée en ce qu'elle comprend des vitamines et/ou oligoéléments.

9. Utilisation cosmétique et non thérapeutique d'au moins une composition telle que définie à l'une quelconque des revendications 1 à 8, pour procurer un effet bronzé à la peau.

10. Utilisation selon la revendication 9, caractérisée en ce que la composition est administrée par voie orale

11. Utilisation selon la revendication 10, caractérisée en ce que la composition est administrée à raison de 1 à 2 capsules par jour.

12. Utilisation selon la revendication 10 ou 11, caractérisée en ce la composition est administrée en une seule prise par jour.

13. Utilisation selon la revendication 9, caractérisée en ce que la composition est administrée par application topique.

14. Composition selon l'une quelconque des revendications 1 à 8, pour une utilisation dans la prévention de l'érythème solaire.

15. Composition pour une utilisation selon la revendication 14 pour une administration par voie orale.

LETTRE AU CLIENT

Dans sa lettre au client, le candidat se devait d'aborder les points suivants :

1. Justifier le choix du ratio carotène/lycopène comme caractéristique essentielle de la revendication 1 de composition en expliquant qu'il découlait de l'analyse de l'art antérieur et que ce ratio permettait de démontrer l'activité inventive de la composition au vu des résultats présentés dans le tableau 2 et dans l'histogramme ;

2. Rappeler que le dépôt de la demande de brevet doit intervenir avant la commercialisation et toute communication publicitaire sur le produit, de préférence avant l'été ;

3. Proposer de déposer une autre demande de brevet pour :
   a. Utilisation cosmétique et non thérapeutique par voie topique d'une composition comprenant du carotène et du lycopène, pour procurer à la peau un effet bronzé. Dans ce cas le dépôt devra intervenir le même jour que la demande principale. **ET/OU**
   b. Procédé pour procurer à la peau un effet bronzé, comprenant une étape d'application sur la peau d'au moins une composition comprenant du carotène et du lycopène. Dans ce cas le dépôt devra intervenir le même jour que la demande principale. **OU**
   c. Composition cosmétique à application topique comprenant du carotène et du lycopène et au moins un excipient cosmétique adaptée à une application par voie topique. Dans ce cas un dépôt ultérieur par rapport à la demande principale est possible mais celui-ci devra être fait avant la publication de la première demande (nouveauté OK grâce à la présence de l'excipient pour application topique).

   A noter que pour les 3 options ci-dessus, la présence du ratio carotène/lycopène tel que défini précédemment pour la demande principale n'est pas commun aux compositions 3 et 5 qui conduisent à une coloration après application topique. C'est pourquoi une demande de brevet séparée doit être envisagée pour protéger cet aspect.

4. Demander des compléments d'information pour cette autre demande.

Instructions aux candidats

DEUXIEME EPREUVE ECRITE

Dans cette épreuve, le candidat doit supposer qu'il a reçu de son client le courrier annexé au sujet, qui comporte la description d'un problème relatif à la validité, à la contrefaçon et/ou à la procédure de délivrance d'un brevet applicable au territoire français, ainsi qu'une copie au moins partielle de ce brevet, le cas échéant, des renseignements et/ou documents reflétant l'état de la technique le plus pertinent et des agissements contestés dont le client a connaissance à l'égard du brevet en question.

Le candidat doit accepter les faits exposés dans le sujet de l'épreuve et fonder ses réponses sur ces faits. Il décide sous sa propre responsabilité s'il fait usage de ces faits, et dans quelle mesure.

Le candidat doit admettre que l'état de la technique, dans le domaine spécifique de l'invention qui fait l'objet du brevet précédemment évoqué, est effectivement celui qui est indiqué dans le sujet et/ou les documents annexes, et que cet état de la technique, le cas échéant complété des connaissances générales nécessaires sur lesquelles il pourrait s'appuyer de façon implicite, est exhaustif.

Il est demandé au candidat de rédiger, sous la forme d'une consultation, un avis sur le problème soumis par son client, en y incluant l'indication de toutes solutions et procédures qu'il pourrait recommander à ce dernier.

Le candidat devra, dans la rédaction de cet avis, identifier de façon complète et non ambiguë les bases factuelles et juridiques de ses conclusions, veiller à exposer clairement le raisonnement qui l'y conduit, et évaluer l'efficacité prévisible de chacune des voies et/ou possibilités de solution qu'il aura envisagées, en les hiérarchisant par degré de pertinence et d'efficacité, afin d'aider son client dans sa prise de décision.

Pour des raisons d'efficacité de rédaction et de lisibilité de cette consultation, il est recommandé au candidat d'éviter de recopier de longs extraits des documents annexés au sujet ou de textes législatifs ou réglementaires, les éléments de fait ou de droit nécessaires à la compréhension de l'argumentation étant de préférence identifiés par localisation des pages et paragraphes pertinents de ces documents et par référence aux numéros des articles applicables.

SUJET DE LA DEUXIEME EPREUVE ECRITE

Monsieur Dandy, Président Directeur Général de la société française GENERICS dont le siège social est implanté en Ile-de-France, vous contacte aujourd'hui avec Monsieur Balta.

Monsieur Balta est pharmacien responsable et directeur de l'usine de production de la société GENERICS basée en Normandie.

GENERICS s'apprête à lancer un médicament générique de la spécialité Algo® HCT (voir D5 publié en décembre 2003). GENERICS a obtenu l'AMM (Autorisation de Mise sur le Marché) et le prix auprès de l'ANSM (Agence Nationale de Sécurité du Médicament et des produits de Santé) donnant le feu vert à la commercialisation.

Le dossier d'AMM est archivé en un seul lieu : au siège social.

Hier, M. Balta a eu la surprise de recevoir en son usine normande un huissier (M. TRUCMUCHE) à 9h le matin accompagné d'un Conseil en Propriété Industrielle (M. DUCHMOLE). M. Balta a vérifié leurs identités. Ceux-ci ont déclaré venir procéder à une saisie-contrefaçon dans les locaux de production.

Ils ont remis à 9h05 à M. Balta copie de la requête et de l'ordonnance de saisie-contrefaçon ainsi que du brevet EP 1 444 444 B1. M. Balta a vérifié que ce brevet est bien cité dans la requête et l'ordonnance de saisie-contrefaçon. Les opérations de saisie ont commencé à 9h10.

M. Balta vous indique que sur demande de l'huissier il a déclaré que GENERICS s'apprête à lancer un médicament générique de la spécialité Algo® HCT et que ce générique est en cours de production.

M. Balta a également déclaré les éléments suivants qui apparaissent dans le procès-verbal de saisie-contrefaçon.

INDIAGEN est une société indienne basée en Inde et spécialisée dans la production de principes actifs.

INDIAGEN prépare des granulés d'algosartan amorphe, hydroxyde de sodium, povidone et lysine de la façon suivante :

- une solution aqueuse d'algosartan amorphe, d'hydroxyde de sodium, de povidone et de lysine est préparée,
- la solution est pulvérisée dans un sécheur par pulvérisation,
- la poudre de granulés sèche est tamisée

GENERICS importe en France les granulés préparés en Inde par INDIAGEN.

GENERICS mélange les granulés d'INDIAGEN avec du sorbitol dans l'eau puis mélange ce prémélange avec du stéarate de magnésium pour obtenir un mélange final (1) pour la première couche de comprimé.

D'autre part, GENERICS prépare une seconde couche de comprimé en :

- mélangeant l'hydrochlorothiazide avec différents excipients utilisés pour préparer des matrices de comprimés désintégrantes,
- ajoutant un lubrifiant pour obtenir un mélange final (2) pour la deuxième couche de comprimé.

Avec les mélanges (1) et (2) GENERICS prépare un comprimé bicouche dans une presse à comprimés.

M. Balta vous précise que Messieurs TRUCMUCHE et DUCHMOLE ont demandé à visiter l'usine et en particulier à voir les lignes de production. M. DUCHMOLE a opéré un prélèvement dans un fût de granulés en provenance d'INDIAGEN avec des ustensiles et contenants qu'il avait lui-même amenés.

M. Balta vous enverra le procès-verbal de saisie-contrefaçon dans quelques jours. Il vous précise que l'huissier a joint à ce PV une facture de la société INDIAGEN à GENERICS pour le produit en question.

QUESTIONS

Monsieur Dandy vous demande :

1. Votre avis sur la validité du brevet européen EP 1 444 444.
2. Votre avis sur la réalité de la contrefaçon en France et les risques auxquels s'exposent les sociétés GENERICS et INDIAGEN vis-à-vis du brevet européen EP 1 444 444.
3. Votre avis sur le déroulement de la saisie-contrefaçon qu'il a subie au vu des éléments qu'il vous expose. Qu'allez-vous vérifier dans le PV de saisie-contrefaçon ?

   Au vu des informations dont vous disposez aujourd'hui, quels sont les éléments qui pourraient permettre de contester le PV et/ou la saisie-contrefaçon ?
4. Quels sont les prochains événements auxquels il doit s'attendre ?

Documents accompagnant le présent sujet

- EP 1 444 444 B1
- D1 : WO 00/22222
- D2 : ALGO®
- D3 : HydroDIURIL®
- D4 : Comparison of the Antihypertensive effects of a fixed dose combination of algosartan and hydrochlorothiazide versus algosartan monotherapy in mild to moderate hypertensive patients
- D5 : Algo® HCT

Lexique

HCTZ ou HCT = hydrochlorothiazide
BP = blood pressure = pression artérielle
FDC = fixed-dose combination = combinaison à dose fixe
Adverse events = effets secondaires

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 444 444 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
12.12.2007 Bulletin 2007/50

(21) Application number: **02777777.8**

(22) Date of filing: **6.02.2002**

(51) Int Cl.:
A61K 9/20 *(2006.01)* ***A61 K 31/635*** *(2006.01)*
A61K 31/54 *(2006.01)* ***A61 K 31/495*** *(2006.01)*
A61K 31/415 *(2006.01)*

(86) International application number:
PCT/EP2002/000333

(87) International publication number:
WO 2003/055555 (4.07.2003 Gazette 2003/30)

(54) **BILAYER PHARMACEUTICAL TABLET COMPRISING ALGOSARTAN AND HYDROCHLOROTHIAZIDE**

ZWEISCHICHTIGE PHARMAZEUTISCHE TABLETTE ENTHALTEND ALGOSARTAN UND HYDROCHLOROTHIAZID

COMPRIME PHARMACEUTIQUE BICOUCHE COMPRENANT ALGOSARTAN ET HYDROCHLOROTHIAZIDE ET PREPARATION DUDIT COMPRIME

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
Designated Extension States:
LT LV

(60) Divisional application:
07777777.1 / 1 888 000

(73) Proprietor: **Algus pharmaceutical Ltd**
Manchester (UK)

(72) Inventors:
- **RIEDL, Thomas**
  Manchester (UK)
- **HICK, Geoffrey**
  Manchester (UK)

(56) References cited:
WO-A-00/22222 **WO-A-99/47123**

- **ALCOUFIERE Y ET AL: "COMPARISON OF THE ANTIHYPERTENSIVE EFFECTS OF A FIXED DOSE COMBINATION OF ALGOSARTAN AND HYDROCHLOROTHIAZIDE VERSUS ALGOSARTAN MONOTHERAPY IN MILD TO MODERATE HYPERTENSIVE PATIENTS" CANADIAN JOURNAL OF CARDIOLOGY, PULSUS GROUP, INC, XX, vol. 16, no. SUPPL F, September 2000 (2000-09), page 107F XP004367890 ISSN: 0828-282X**

EP 1 444 444 B1

Description

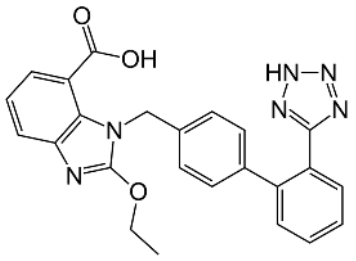
Field of invention

[0001] The present invention relates to a bilayer pharmaceutical tablet formulation comprising the angiotensin II receptor antagonist algosartan in combination with the diuretic hydrochlorothiazide (HCTZ). The present invention also provides a method of producing said bilayer tablet.

Background of the invention

[0002] INN Algosartan is an angiotensin II receptor antagonist developed for the treatment of hypertension and other medical indications as disclosed in EP-A-522 222.

[0003] Its chemical name is 1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid having the following structure:



[0004] Algosartan is generally manufactured and supplied in the free acid form. It is characterized by its very poor solubility in aqueous systems at the physiological pH range of the gastro-intestinal tract of between pH 1 to 7. As disclosed in WO 00/42000, crystalline algosartan exists in two polymorphic forms having different melting points. Under the influence of heat and humidity, the lower melting polymorph B transforms Irreversibly into the higher melting polymorph A.

[0005] Hydrochlorothiazide (HCTZ) is a thiazide diuretic which is orally administered in the treatment of edema and hypertension.

[0006] The chemical name of HCTZ is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide having the following structure

Alcoufière et al (Can J Cardiol 16 (suppl F): 107F, 2000) describe that a fixed dose combination of algosartan and HCTZ confers additional blood pressure reductions.

Objects of the Invention

[0007] Combination therapy of algosartan with a diuretic like HCTZ is expected to show synergistic therapeutic efficacy in the treatment of hypertension.

[0008] It was therefore an object of the present invention to provide a fixed dose combination drug comprising algosartan and the diuretic HCTZ, said combination drug displaying the required fast dissolution and immediate drug release profile combined with adequate stability.

[0009] Generally, a fixed-dose combination of drugs intended for immediate release is prepared by either making a powder mixture or a co-granulate of the two active ingredients with the necessary excipients, normally keeping the basic

formulation of the corresponding mono-drug preparation and simply adding the second drug component.

[0010] With a combination of algosartan and HCTZ, this approach was not feasible due to the incompatibility of HCTZ with basic compounds such as, e.g., lysine which is a component of conventional algosartan' formulations, and the reduced dissolution rate of HCTZ from a dissolving matrix as compared with dissolution from a disintegrating tablet.

[0011] Several galenical approaches to overcome the incompatibility problem have been investigated. A classical approach is to coat the HCTZ particles in a fluidized-bed granulator with a polymer solution containing water soluble polymers like hydroxypropylcellulose, hydroxypropylmethylcellulose or polyvinylpyrrolidone, thereby reducing the contact surface area of the HCTZ particles with the algosartan formulation during mixing and compressing. Yet, by these means it was not possible to reduce the contact area of HCTZ with the algosartan formulation in a compressed tablet to a degree sufficient to achieve the desired prolonged shelf life.

[0012] Furthermore, the dissolution rate of HCTZ from tablets comprising coated HCTZ in an algosartan formulation was further reduced due to the get-forming properties of the polymer.

[0013] Another approach was to produce separate film-coated tablets for algosartan and HCTZ in such a size and shape that these could be filled into a capsule. By dividing the doses into two to four single small tablets for algosartan and into one or two small tablets for HCTZ, a capsule of size 1 to 0 long could be filled. Yet, with this approach the drug dissolution rate of algosartan was reduced compared to the single entities due to a lag-time effect of the large capsule shells. Furthermore, with regard to patients compliance a zero long capsule is not deemed reliable.

Summary of the invention

[0014] In accordance with the present invention, is has now been found that the above-described problems associated with conventional approaches in the preparation of a fixed dose combination drug comprising algosartan and HCTZ could be overcome by means of a bilayer pharmaceutical tablet comprising a first layer containing algosartan in substantially amorphous form in a dissolving tablet matrix comprising a basic agent and a water soluble diluent, and a second layer containing HCTZ in a disintregrating tablet matrix.

[0015] The bilayer tablet according to the present invention provides a largely pH-independent dissolution of the poorly water-soluble algosartan, thereby facilitating dissolution of the drug at a physiological pH level, and also provides for immediate release of the diuretic from the fast disintegrating matrix. At the same time, the bilayer tablet structure overcomes the stability problem caused by the incompatibility of diuretics like HCTZ with basic constituents of the algosartan formulation.

[0016] In a further aspect, the present invention relates to an improvement in bilayer tableting technology and provides a method of producing a bilayer pharmaceutical tablet comprising the steps of:

(i) providing a first tablet layer composition by

a) preparing an aqueous solution of algosartan, at least one basic agent and, optionally, a solubilizer and a crystallization retarder;
b) spray-drying said aqueous solution to obtain a spray-dried granulate;
c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
d) mixing said premix with a lubricant to obtain a final blend for the first tablet layer;
e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

f) mixing and/or granulating HCTZ with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;
g) admixing a lubricant to obtain a final blend for the second tablet layer;

(iii) introducing the first or the second tablet layer composition in a tablet press;
(iv) compressing said tablet layer composition to form a tablet layer;
(v) introducing the other tablet layer composition into the tablet press; and
(vi) compressing both tablet layer compositions to form a bilayer tablet.

Definitions

[0017] As used herein, the term "substantially amorphous" refers to a product comprising amorphous constituents in a proportion of at least 90%, preferably at least 95%, as determined by X-ray powder diffraction measurement.

[0018] The term "dissolving tablet matrix" refers to a pharmaceutical tablet base formulation having immediate release (fast dissolution) characteristics that readily dissolves in a physiological aqueous medium.

[0019] The term "disintegrating tablet matrix" refers to a pharmaceutical tablet base formulation having immediate release characteristics that readily swells and disintegrates in a physiological aqueous medium.

Description of the preferred embodiments

[0020] The bilayer tablet according to the present invention comprises a first layer containing algosartan in substantially amorphous form in a dissolving tablet matrix, and a second layer containing the diuretic HCTZ in a disintregrating tablet matrix.

[0021] The active ingredient algosartan is generally supplied in its free acid form, although pharmaceutically acceptable salts may also be used. Since during subsequent processing algosartan is normally dissolved and transformed into a substantially amorphous form, its initial crystal morphology and particle size are of little importance for the physical and biopharmaceutical properties of the bilayer tablet formulation obtained. It is however preferred to remove agglomerates from the starting material, e.g. by sieving, in order to facilitate wetting and dissolution during further processing.

[0022] The use of amorphous form is very attractive for this poorly soluble compound because of the enhanced solubility and dissolution rate over the crystalline state leading to increased bioavailability.

[0023] Substantially amorphous algosartan may be produced by any suitable method known to those skilled in the art, for Instance, by freeze drying of aqueous solutions, coating of carrier particles in a fluidized bed, and solvent deposition on sugar pellets or other carriers. Preferably, however, the substantially amorphous algosartan is prepared by the specific spray-drying method described hereinafter. The use of a crystallization retarder is also of importance to maintain algosartan in substantially amorphous form.

[0024] The other active ingredient HCTZ is usually employed as a fine-crystalline powder, optionally in fine-milled, peg-milled or micronized form. For instance, the particle size distribution of hydrochlorothiazide, as determined by the method of laser light scattering in a dry dispersion system (Sympatec Helos/Rodos, focal length 100 mm) is preferably as follows:

d_{10} : 20 µm, preferably 2 to 10 µm
d_{50} : 5 to 50 µm, preferably 10 to 30 µm
d_{90} : 20 to 100 µm, preferably 40 to 80 µm

[0025] The bilayer tablet according to the present invention generally contains 10 to 160 mg, preferably 20 to 80 mg, of algosartan and 6.25 to 50 mg, preferably 12.5 to 25 mg, of HCTZ. Presently preferred forms are bilayer tablets comprising 40/12.5 mg, 80/12.5 mg and 80/25 mg of algosartan and HCTZ, respectively.

[0026] The first tablet layer contains algosartan in substantially amorphous form dispersed in a dissolving tablet matrix having immediate release (fast dissolution) characteristics. The dissolving tablet matrix has basic properties.

[0027] The dissolving matrix comprises a basic agent, a water-soluble diluent and, optionally, other excipients and adjuvants.

[0028] Specific examples of suitable basic agents are alkali metal hydroxides such as NaOH and KOH; basic amino acids such as arginine and lysine; and meglumine (N-methyl-D-glucamine), NaOH and lysine being preferred.

[0029] Specific examples of suitable water-soluble diluents are carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose, anhydrous lactose and lactose monohydrate; and sugar alcohols like sorbitol, mannitol, dulcitol, ribitol and xylitol. Sorbitol is a preferred diluent.

[0030] The other excipients and/or adjuvants are, for instance, selected from binders, carriers, fillers, lubricants, flow control agents, crystallization retarders, solubilizers, coloring agents, pH control agents, surfactants and emulsifiers, specific examples of which are given below in connection with the second tablet layer composition. The excipients and/or adjuvants for the first tablet layer composition are preferably chosen such that a non-acidic, fast dissolving tablet matrix is obtained.

[0031] The first tablet layer composition generally comprises 3 to 50 wt.%, preferably 5 to 35 wt.%, of active ingredient; 0.25 to 20 wt.%, preferably 0.40 to 15 wt.%, of basic agent; and 30 to 95 wt.%, preferably 60 to 80 wt.% of water-soluble diluent.

[0032] Other (optional) constituents may, for instance, be chosen from one or more of the following excipients and/or adjuvants in the amounts indicated:

10 to 30 wt.%, preferably 15 to 25 wt.%, of binders, carriers and fillers, thereby replacing the water-soluble diluent;
0.1 to 5 wt.%, preferably 0.5 to 3 wt.%, of lubricants;
0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, of flow control agents;
1 to 10 wt.%, preferably 2 to 8 wt.%, of crystallization retarders;
1 to 10 wt.%, preferably 2 to 8 wt.% of solubilizers;
0.05 to 1.5 wt.%, preferably 0.1 to 0.8 wt.%, of coloring agents;
0.5 to 10 wt.%, preferably 2 to 8 wt.%, of pH control agents;
0.01 to 5 wt.%, preferably 0.05 to 1 wt.%, of surfactants and emulsifiers.

[0033] The second tablet layer composition contains HCTZ in a fast disintegrating tablet matrix. In a preferred embodiment, the disintegrating tablet matrix comprises a filler, a binder, a disintegrant and, optionally, other excipients and adjuvants.

[0034] The filler is preferably selected from anhydrous lactose, spray-dried lactose and lactose monohydrate.

[0035] The binder is selected from the group of dry binders and/or the group of wet granulation binders, depending on the manufacturing process chosen for the second tablet layer. Suitable dry binders are, e.g., cellulose powder and microcrystalline cellulose. Specific examples of wet granulation binders are com starch, polyvinyl pyrrolidone (Povidon), vinylpyrrolidone-vinylacetate copolymer (Copovidone) and cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose.

[0036] Suitable disintegrants are, e.g., sodium starch glycolate, Crospovidon, Croscarmellose, sodium carboxymethylcellulose and dried com starch, sodium starch glycolate being preferred.

[0037] The other excipients and adjuvants, if used, are preferably selected from diluents and carriers such as cellulose powder, microcrystalline cellulose, cellulose derivatives like hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, dibasic calcium phosphate, com starch, pregelatinized starch, polyvinyl pyrrolidone (Povidone) etc.; lubricants such as stearic acid, magnesium stearate, sodium stearylfumarate, glycerol tribehenate, etc.; flow control agents such as colloidal silica, talc, etc.; crystallization retarders such as Povidone, etc.; solubilizers such as Pluronic, Povidone, etc.; coloring agents, including dyes and pigments such as Iron Oxide Red or Yellow, titanium dioxide, talc, etc.; pH control agents such as citric acid, tartaric acid, fumaric acid, sodium citrate, dibasic calcium phosphate, dibasic sodium phosphate, etc.; surfactants and emulsifiers such as Pluronic, polyethylene glycols, sodium carboxymethyl cellulose, polyethoxylated and hydrogenated castor oil, etc.; and mixtures of two or more of these excipients and/or adjuvants.

[0038] The second tablet layer composition generally comprises 1.5 to 35 wt.%, preferably 2 to 15 wt.%, of active ingredient; 25 to 75 wt.%, preferably 35 to 65 wt.%, of filler; 10 to 40 wt.%, preferably 15 to 35 wt.%, of dry binder; 0.5 to 5 wt.%, preferably 1 to 4 wt.%, of wet granulation binder; and 1 to 10 wt.%, preferably 2 to 8 wt.%, of disintegrant. The other excipients and adjuvants are generally employed in the same amount as in the first tablet layer composition.

[0039] For preparing the bilayer tablet according to the present invention, the first and second tablet layer compositions may be compressed in the usual manner in a bilayer tablet press, e.g. a high-speed rotary press in a bilayer tableting mode. However, care should be taken not to employ an excessive compression force for the first tablet layer. Preferably, the ratio of the compression force applied during compression of the first tablet layer to the compression force applied during compression of both the first and second tablet layers is in the range of from 1:10 to 1:2. For instance, the first tablet layer may be compressed at moderate force of 4 to 8 kN, whereas the main compression of first plus second layer is performed at a force of 10 to 20 kN.

[0040] During bilayer tablet compression adequate bond formation between the two layers is achieved by virtue of distance attraction forces (intermolecular forces) and mechanical interlocking between the particles.

[0041] The bilayer tablets obtained release the active ingredients rapidly and in a largely pH-independent fashion, with complete release occurring within less than 60 min and release of the major fraction occurring within less than 15 min. The dissolution/disintegration kinetics of the bilayer tablet may be controlled in different ways. For instance, both layers may dissolve/disintegrate simultaneously. Preferably, however, the second tablet layer containing the diuretic disintegrates first whereas the first tablet layer containing algosartan dissolves in parallel or subsequently.

[0042] In accordance with the present invention, a substantially increased dissolution rate of the active ingredients and, in particular, of algosartan is achieved. Normally, at least 70% and typically at least 90% of the drug load are dissolved after 30 min.

[0043] The bilayer tablets of the present invention tend to be slightly hygroscopic and are therefore preferably packaged using a moisture-proof packaging material such as aluminium foil blister packs, or polypropylene tubes and HDPE bottles which preferably contain a desiccant.

[0044] For optimum dissection/disintegration and drug release properties, a specific method of producing the bilayer tablet according to the present invention has been developed which method comprises

(i) providing a first tablet layer composition by

a) preparing an aqueous solution of algosartan, at least one basic agent and a solubilizer and a crystallization retarder;
b) spray-drying said aqueous solution to obtain a spray-dried granulate;
c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
d) mixing said premix with a lubricant to obtain a final blend for the first layer;
e) optionally, adding other excipients and/or adjuvants in any of steps a) to d);

(ii) providing a second tablet layer composition by

f) mixing and /or granulating HCTZ with the constituents of a disintegrating tablet matrix and, optionally, further excipients and/or adjuvants;
g) admixing a lubricant to obtain a final blend for the second tablet layer,

(iii) introducing the first or the second tablet layer composition into a tablet press;
(iv) compressing said tablet layer composition to form a tablet layer;
(v) introducing the other tablet layer composition into the tablet press; and
(vi) compressing both tablet layer compositions to form a bilayer tablet

[0045] In a preferred embodiment of this method, an aqueous alkaline solution of algosartan is prepared by dissolving the active ingredient in purified water with the help of one or more basic agents like sodium hydroxide and lysine. A solubilizer and a recrystallization retarder may be added. The dry mater content of the starting aqueous solution is generally 10 to 40 wt.%, preferably 20 to 30 wt.%.

[0046] **T**he aqueous solution is then spray-dried at room temperature or preferably at increased temperatures of, for instance, between 50 and 100°C in a co-current or countercurrent spray-drier at a spray pressure of, for instance, 1 to 4 bar (1000-4000 hPa). Generally speaking, the spray-drying conditions are preferably chosen in such a manner that a spray-dried granulate having a residual humidity of 5 wt.%, preferably 3.5 wt.%, is obtained in the separation cyclone. To that end, the outlet air temperature of the spray-drier is preferably kept at a value of between about 80 and 90°C while the other process parameters such as spray pressure, spraying rate, inlet air temperature, etc. are adjusted accordingly.

[0047] The spray-dried granulate obtained is preferably a fine powder having the following particle size distribution:

d_{10} : 20 µm, preferably 10 µm
d_{50} : 80 µm, preferably 20 to 55 µm
d_{90} : 350 µm, preferably 50 to 150 µm

[0048] After spray-drying, the active ingredient (algosartan) as well as the excipients contained in the spray-dried granulate are in a substantially amorphous state with no crystallinity being detectable. From a physical point of view, the spray-dried granulate is a solidified solution or glass having a glass transition temperature Tg of preferably > 50°C, more preferably > 80°C.

[0049] Based on 100 parts by weight of active ingredient (algosartan), the spray-dried granulate preferably contains 5 to 200 parts by weight of basic agent and, optionally, solubilizer and/or crystallization retarder.

[0050] The water-soluble diluent is generally employed in an amount of 30 to 95 wt.%, preferably 60 to 80 wt.%, based on the weight of the first tablet layer composition.

[0051] The lubricant is generally added to the premix in an amount of 0.1 to 5 wt.%, preferably 0.3 to 2 wt.%, based on the weight of the first tablet layer composition.

[0052] Mixing is carried out in two stages, i.e. in a first mixing step the spray-dried granulate and the diluent are admixed using, e.g., a high-shear mixer or a free-fall blender, and in a second mixing step the lubricant is blended with the premix, preferably also under conditions of high shear. The method of the invention is however not limited to these mixing procedures and, generally, alternative mixing procedures may be employed in steps c), d), and also in the subsequent steps f) and g), such as, e.g., container mixing with intermediate screening.

[0053] For direct compression, the second tablet layer composition may be prepared by dry-mixing the constituent components, e.g. by means of a high-intensity mixer or a free-fall blender. Alternatively, and preferably, the second tablet layer composition is prepared using a wet granulation technique wherein an aqueous solution of a wet granulation binder is added to a premix and subsequently the wet granulate obtained is dried, e.g. in a fluidized-bed dryer or drying chamber. The dried mixture is screened and then a lubricant is admixed, e.g. using a tumbling mixer or free-fall blender, whereafter the composition is ready for compression.

[0054] For production of the bilayer tablet according to the present invention, the first and second tablet layer compositions are compressed in a bilayer tablet press, e.g. a rotary press in the bilayer tableting mode, in the manner described above. In order to avoid any cross-contamination between the first and second tablet layers (which could lead to de-composition of HTCZ), any granulate residues have to be carefully removed during tableting by intense suction of the die table within the tableting chamber.

[0055] In order to further illustrate the present invention, the following examples are given.

Example 1

[0056]

Constituents		mg / 1.684 mg SD granulate	volatile constituent	kg / batch
(01)	Algosartan	1.000		45.000
(02)	Sodium hydroxide	0.084		3.780
(03)	Povidone K 25	0.300		13.500
(04)	Lysine	0.300		13.500
(05)	Purified water		5.000	(225.000)
		1.684	5.000	75.780

Manufacturing:

1. Spray solution

[0057] 225.000 kg of purified water are measured into a suitable stainless steel vessel at a temperature of between 20-40°C. In sequence, 3.780 of kg sodium hydroxide, 45.000 kg of algosartan (mixture of polymorph A and B), 13.500 kg of Povidone K 25 and 13.500 kg of lysine are dissolved in the purified water under intensive stirring until a virtually clear, slightly yellowish, alkaline solution is obtained.

2. Spray drying

[0058] The solution is sprayed into a suitable spray dryer, e.g. a Niro P 6.3 equipped with Schlick atomizing nozzles of 1.0 mm diameter, with a flow-through heating coil connected upstream of the dryer, and dried to give a white to off-white fine granulate. The spray mode is counter-current at a spray-pressure of about 3 bar (3000 hPa), an inlet air temperature of about 125°C and a spray rate of about 11 kg/h, thus resulting in an outlet air temperature of about 85°C. The temperature of the flow through heating coil water bath is set at a temperature of about 80°C.

3. Protective Screening

[0059] The dry granulate powder is screened through a screen of 0.5 mm mesh size, e.g. using a Vibra Sieve machine.
[0060] The resulting amorphous algosartan spray-dried granulate may be further processed to the first layer of the said bilayer tablet composition.

Example 2

[0061]

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Algosartan SD granulate	67.360		
	consisting of (02) to 06):			
(02)	Algosartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone (Kollidon 25)		12.000	
(05)	Lysine		12.000	
(06)	Purified water		264.000*	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000

(continued)

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(09)	Hydrochlorothiazide			12.500
(10)	Microcrystalline cellulose (Avicel PH 101)			64.000
(11)	Red iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine, screened			112.170
(14)	Maize starch, dried at 45°C			6.000
		240.000	67.360	200.000
*200 mg in SD granulate, 64 mg in granulation liquid of HCTZ granulate				

Manufacturing:

1. Final blend A

[0062] 168.640 kg of sorbitol are mixed with 67.360 kg of algosartan spray dried granulate in a suitable high shear mixer, e.g. Diosna P 600, for 4 minutes using both impeller and chopper. Next 4.0 kg of magnesium stearate are added to the resulting pre-mix and admixed in the high shear mixer for further 30 seconds.

2. Final blend B

[0063] 9.000 kg of purified water of about 70°C are transferred to a suitable mixing vessel, 6.000 kg of maize starch, dried at 45°C, are suspended in the water. This suspension is stirred into 55.000 kg of purified water of about 90°C using e.g. an Ekato stirrer.

[0064] Next, 112.170 kg of lactose monohydrate, 12.500 kg of hydrochlorothiazide, 64.000 kg of microcrystalline cellulose (Avicel PH 101), 0.330 kg of red iron oxide and 4.000 kg of sodium starch glycolate are mixed in a suitable high shear granulator, e.g. Diosna P 600, until homogeneous, and moistened with 70.000 kg of the above-prepared aqueous granulating liquid.

[0065] Process parameters for wet granulation:

Process step	Duration (min)	Impeller (setting)	Chopper (setting)
Pre-mixing	3	1	1
Moistening	2	1	1
Wet mixing	4	2	2
Emptying	About 0.5	1	0

[0066] After moistening, the resulting wet granulate is dried in a suitable fluid bed dryer, e.g. Glatt WSG 120 at an inlet air temperature of 100°C, an inlet air flow of 2000-3000 m^3/h until a product temperature of about 55°C is reached.

[0067] The dry granulate is screened to reduce the particle size using a suitable screening machine, e.g. a Comil screen machine equipped with a rasp screen of 2 mm mesh size. Finally, 1.000 kg of prescreened magnesium stearate are admixed to the screened granulate material and mixed in a suitable tumbling mixer, e.g. a Lermer rotating spike mixer, for 100 revolutions at a speed of 8-10 rpm.

3. Bilayer tablet compression

[0068] Using a suitable rotary tablet press, 240 kg of the final blend (A) and 200 kg of the final blend (B) are compressed into bilayer tablets. The target weight for the first layer is 240 mg, the target weight for the second layer is 200 mg.

[0069] Process parameters for tableting:

Tablet press	Fette 3090	
Tabletting speed	100.000 (80.000 -120.000) tabl./h	
Stirrer blade speed:	1 st layer about 30 rpm	2nd layer about 75 rpm
Compression force	5 (4 - 6) kN	12 (10 - 14) kN

[0070] As a rule, the tablet hardness is adjusted by variation of the main compression force of the second layer.
[0071] The resulting bilayer tablets have the following characteristics:

Shape / diameter	oval, both faces convex /14 x 6.8 mm
Colour	first layer: white to off-white second layer: red
Weight	440 mg (total) 240 mg (layer 1: with algosartan) 200 mg (layer 2: with hydrochlorothiazide)
Thickness	about 5.2 mm
Hardness	about 120 N
Disintegration time	NMT 15 min (total)

Example 3

[0072]

	Constituents	mg/tablet 1st layer	mg/SD granulate	mg/tablet 2nd layer
(01)	Algosartan SD granulate	67.360		
	consisting of (02) to (06):			
(02)	Algosartan		40.000	
(03)	Sodium hydroxide		3.360	
(04)	Polyvidone (Kollidon 25)		12.000	
(05)	Lysine		12.000	
(06)	Purified water		(200.000)	
(07)	Sorbitol P/6	168.640		
(08)	Magnesium stearate, screened	4.000		1.000
(09)	Hydrochlorothiazide			25.000
(10)	Microcrystalline cellulose (Avicel PH 101)			64.000
(11)	Yellow iron oxide			0.330
(12)	Sodium starch glycolate			4.000
(13)	Lactose monohydrate fine, screened			105.67
		240.000	67.360	200.000

Manufacturing:

[0073] Manufacturing is carried out as in Example 2. Instead of the wet granulation process described in Example 2, the second layer composition is manufactured by dry mixing of (09) to (13) in a suitable free fall blender, e.g. a 1 m^3

container mixer, for 200 revolutions at a speed of 10 rpm. Then, (08) is admixed to the main mixture for further 50 revolutions in the container mixer. In order to achieve a homogenous distribution of the color pigment, an additional premix with yellow iron oxide and a portion of the microcrystalline cellulose, e.g. 2.000 kg, which is screened through an 0.8 mm mesh screen manually before transfer to the main mixture, may be performed. The resulting bilayer tablets display virtually the same physical characteristics as described in example 2, except for the color.

Example 4

[0074] Composition of Telmisartan/Hydrochlorothiazide Bilayer Tablets (mg per tablet):

Ingredient	40/12.5 mg	80/12.5 mg
Algosartan layer		
Algosartan	40.000	80.000
Sodium hydroxide	3.360	6.720
Povidone	12.000	24.000
Lysine	12.000	24.000
Purified water*	(200.000)	(400.000)
Sorbitol	168.640	337.280
Magnesium stearate	4.000	8.000
Total algosartan layer	240.000	480.000
Hydrochlorothiazide layer		
Hydrochlorothiazide	12.500	12.500
Lactose monohydrate	112.170	112.170
Microcrystalline Cellulose	64.000	64.000
Corn starch	6.000	6.000
Red iron oxide	0.330	0.330
Sodium starch glycolate	4.000	4.000
Purified water*	(64.000)	(64.000)
Magnesium stearate	1.000	1.000
Total HCTZ layer	200.000	200.000
Total tablet weight	440.000	680.000
*Does not appear in final product		

Claims

1. A bilayer pharmaceutical tablet comprising a first layer containing algosartan in at least 90% amorphous form in a dissolving tablet matrix comprising a basic agent and a water soluble diluent, and a second layer containing hydro-chlorothiazide in a disintegrating tablet matrix.

2. A bilayer pharmaceutical tablet as claimed in claim 1 where the basic agent is selected from alkali metal hydroxides, arginine, lysine and meglumine.

3. A bilayer pharmaceutical tablet as claimed in claims 1 wherein the water-soluble diluent is selected from carbohydrates such as monosaccharides like glucose; oligosaccharides like sucrose and lactose; and sugar alcohols like sorbitol, mannitol, dulcitol, ribitol and xylitol.

4. A method of producing a bilayer pharmaceutical tablet comprising the steps of:

   (i) providing a first tablet layer composition by

   a) preparing an aqueous solution of algosartan, at least one basic agent and a solubilizer and a crystallization retarder;
   b) spray-drying said aqueous solution to obtain a spray-dried granulate;
   c) mixing said spray-dried granulate with a water-soluble diluent to obtain a premix;
   d) mixing said premix with a lubricant to obtain a final blend for the first tablet layer,

   (ii) providing a second tablet layer composition by

   e) mixing and/or granulating hydrochlorothiazide with the constituents of a disintegrating tablet matrix;
   f) admixing a lubricant to obtain a final blend for the second tablet layer;

   (iii) introducing the first or the second tablet layer composition into a tablet press;
   (iv) compressing said tablet layer composition to form a tablet layer;
   (v) introducing the other tablet layer composition into the tablet press; and
   (vi) compressing both tablet layer compositions to forma bilayer tablet.

5. A bilayer tablet as claimed in any one of claims 1-3 for its use in the treatment of hypertension.

Patentansprüche

1. Zweischichtige pharmazeutische Tablette, umfassend eine erste Schicht, enthaltend Algoisartan in mindestens 90% amorpher Form in einer löslichen Tablettenmatrix, umfassend ein basisches Mittel und ein wasserlösliches Verdünnungsmittel, und eine zweite Schicht, enthaltend Hydrochlorthiazid in einer zerfallenden Tablettenmatrix.

2. Zweischichtige pharmazeutische Tablette nach Anspruch 1, worin das basische Mittel ausgewählt ist aus Alkalimetallhydroxiden, Arginin, Lysin und Meglumin.

3. Zweischichtige pharmazeutische Tablette nach Anspruch 1, worin das wasserlösliche Verdünnungsmittel ausgewählt ist aus Kohlenhydraten, wie Monosacchariden, wie Glucose; Oligosacchariden, wie Saccharose und Lactose; und Zuckeralkoholen, wie Sorbitol, Mannitol, Dulcitol, Ribitol und Xylitol.

4. Verfahren zur Herstellung einer zweischichtigen pharmazeutischen Tablette, umfassend die Schritte:

   (i) Bereitstellen einer ersten Tablettenschichtzusammensetzung durch

   a) Vorbereiten einer wässerigen Lösung von Algosartan, mindestens einem basischen Mittel und einem Lösungshilfsmittel und einem Kristallisationsverzögerern;
   b) Sprühtrocknen der wässerigen Lösung, um ein sprühgetrocknetes Granulat zu erhalten;
   c) Mischen des sprühgetrockneten Granulats mit einem wasserlöslichen Verdünnungsmittel, um eine Vormischung zu erhalten;
   d) Mischen der Vormischung mit einem Schmiermittel, um eine Endmischung für die erste Tablettenschicht zu erhalten;

(ii) Bereitstellen einer zweiten Tablettenschichtzusammensetzung durch

e) Mischen und/oder Granulieren von Hydrochlorthiazid mit den Bestandteilen einer zerfallenden Tablettenmatrix;
f) Zumischen eines Schmiermittels, um eine Endmischung der zweiten Tablettenschicht zu erhalten;

(iii) Einführen der ersten oder der zweiten Tablettenschichtzusammensetzung in eine Tablettenpresse;
(iv) Komprimieren der Tablettenschichtzusammensetzung, um eine Tablettenschicht zu bilden;
(v) Einführen der anderen Tablettenschichtzusammensetzung in die Tablettenpresse; und
(vi) Komprimieren beider Tablettenschichtzusammensetzungen, um eine zweischichtige Tablette zu bilden.

5. Zweischichtige pharmazeutische Tablette nachirgendeinem der Ansprüche 1-3 zur Anwendung bei der Behandlung von Bluthochdruck.

Revendications

1. Comprimé pharmaceutique bicouche comprenant une première couche contenant de l'algosartan sous forme amorphe à au moins 90 % dans une matrice de comprimé dissolvante comprenant un agent basique et un diluant soluble dans l'eau, et une seconde couche contenant de l'hydrochlorothiazide dans une matrice de comprimé désintégrante.

2. Comprimé pharmaceutique bicouche selon la revendication 1 où l'agent basique est choisi parmi les hydroxydes de métaux alcalins, l'arginine, la lysine et la méglumine.

3. Comprimé pharmaceutique bicouche selon la revendication 1 où le diluant soluble dans l'eau est choisi parmi les glucides comme les monosaccharides tels que le glucose ; les oligosaccharides tels que le saccharose et le lactose ; et les alcools de sucre tels que le sorbitol, le mannitol, le dulcitol, le ribitol et le xylitol.

4. Procédé de production d'un comprimé pharmaceutique bicouche comprenant les étapes de :

(i) fournir une composition de première couche de comprimé en :

a) préparant une solution aqueuse d'algosartan, d'au moins un agent basique et d'un solubilisant et un retardateur de cristallisation ;
b) séchant par pulvérisation ladite solution aqueuse pour obtenir des granulés séchés par pulvérisation ;
c) mélangeant lesdits granulés séchés par pulvérisation avec un diluant soluble dans l'eau pour obtenir un prémélange ;
d) mélangeant ledit prémélange avec un lubrifiant pour obtenir un mélange final pour la première couche de comprimé ;

(ii) fournir une composition de seconde couche de comprimé en

e) mélangeant et/ou granulant de l'hydrochlorothiazide avec les constituants d'une matrice de comprimé désintégrante ;
f) ajoutant un lubrifiant pour obtenir un mélange final pour la seconde couche de comprimé ;

(iii) introduire la composition de première ou de seconde couche de comprimé dans une presse à comprimés ;
(iv) compresser ladite composition de couche de comprimé pour former une couche de comprimé ;
(v) introduire l'autre composition de couche de comprimé dans la presse à comprimés ; et
(vi) compresser les deux compositions de couche de comprimé pour former un comprimé bicouche.

5. Comprimé pharmaceutique bicouche selon l'une quelconque des revendications 1-3 pour son utilisation dans le traitement de l'hypertension.

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PCT WORLD INTBLLECTUAL PROPERTY ORGANIZATION International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER TIIE PATENT COOPERATION TREATY (PCI')

(51) International Patent Classification 6 : A61K 31/44 Al

(11) International Publication Number: WO 00/22222

(43) International Publication Date: 20 May 2000 (20.05.00)

(21) International Application Number: PCT/GB98/33333

(22) International Fillng Date: 6 Novembcr 1998 (06.11.98)

(71) Applicants: SEVRIL LABO SA, FR; ALGUS PHARMACEUTICAL, LTd, UK

(72) Inventor: GAGHI, Giovanni, 37135 Liverpool (UK).

(74) Agent: FJLLER, Wendy, A.; BRIAN Co. Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN (GB).

(81) Deslgnated States: AL, AM, AT, AU, AZ, BA, BB, BO. BR, BY, CA, CH, CN, eu. cz, DE, DK, BE, ES, FI, GB, GD, GE, OH. GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK. MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (OH, GM, KB, LS, MW, SD, SZ. UG, ZW), Euraslan patent (AM, AZ, BY, KG, xz, MD, RU, Tl, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, OR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BP, BJ, CF, CG, Cl, CM, GA, GN, GW, ML, MR, NB, SN, TD, TG).

Published
With international search report.

(54) Title: ANTIHYPERTENSIVE MEDICAMENTS CONTAINING LACIDlPINE AND ALGOSARTAN

(57) Abstract

Combinations comprising diethyl (E) -4-[2r-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dlcarboxylate (lacidipine) and 1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]-benzimidazole-7-carboxylic acid (algosartan), pharmaceutical compositions containing said combinations and their use in the treatment of cardiovascular dlsorders including hypertension.

ANTIHYPERTENSIVE MEDICAMENTS CONTAINING LACIDIPINE AND ALGOSARTAN

The present invention relates to therapeutic combinations comprising diethyl (E)-4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (lacidipine) and 1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]méthyl]benzimidazole-7-carboxylic acid (algosartan), to pharmaceutical compositions containing said combinations and their use in the treatment of cardiovascular disorders including hypertension.

Lacidipine, which is described in British patent no. 2164336 , is a patent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may be aise useful for the treatment of other carcliovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Algosartan, which is described in European patent no. 052222, is an angiotensin-II-antagonist which is useful for treating hypertension and cardiac insufficiency and for treating other cardiovascular disorders including ischaemic peripheral circulation disorders, myocardial ischaemia (angina).

European patent no. 052222 teaches that the angiotensin-11-antagonists described therein may be administered in combination with other active substances including calcium antagonists. There is however no specific disclosure of such combinations with lacidipine.

We have found that the combination of lacidipine and algosartan provides a useful and unexpectedly advantageous combination for the treatment of cardiovascular disorders, such as hypertension, atherosclerosis and ischaemic heart disease.

In particular it has now been found that by combining lacidipine and algosartan, a synergistic antihypertensive effect is achieved.

It is a feature of this invention that the use of such a drug combination will provide one or more of the following effects: synergistic antihypertensive effects, antihypertensive affect over a longer period and/or allow a better management of any potential drug-related side affects.

Furthermore, the improvement of blood pressure control achieved by using such a drug combination may afford a better protection from the associated diseases which are induced by hypertension.

According to one aspect of the invention there is provided a combination comprising lacidipine and algosartan or a physiologically functional derivative thereof and more particularly a combination comprising lacidipine and algosartan.

As used herein, the term *"physiologically functional derivative"* includes any physiologically acceptable solvate, sait, ester, sait of such ester, or solvates of any such sait or ester, of algosartan.

Preferred esters in accordance with the invention are independently selected from the following group: (1) carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy), or amino; (2) sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); and (4) phosphonate esters. In such esters, unless otherwise specified, any

alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable sait thereof.

Examples of physiologically acceptable salts include salts derived from an appropriate base, such as an alkafi metal (for example, sodium), an alkaline earth for example, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4} alkyl) or ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, phenylbenzylamine, ethanolamine and N-methylglucosamine).

Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

The present invention thus provides a method for the treatment of hypertension in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of lacidipine and algosartan or a physiologically functional derivative thereof.

Reference herein to treatment extends to prophylaxis as well as the treatment of established hypertension or symptoms.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second and any subsequent active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be understood that the compounds of the combination or the physiologically functional derivatives of any thereof, whether presented simultaneously or sequentially, may be administered individually or in multiples or in any combination thereof.

According to another aspect, the present invention provides the use of lacidipine in the manufacture of a medicament for administration simultaneously or sequentially with algosartan or a physiologically functional derivative thereof for the treatment and/or prophylaxis of hypertension.

The synergistic effects of the combination of lacidipine and algosartan may be seen over a wide ratio of combinations, for example, of 1: 100 to 1: 1, such as 1:50 to 1:2 (by weight), preferably of 1:40 to 1:3.33(by weight). Examples of such combinations include those wherein the ratio (by weight) of lacidipine to algosartan is 1:5; 1:10, 1:20; 1:40; 1:6.67 or 1: 13.33. Conveniently each compound will be employed in the combination in an amount at which it exhibits an antihypertensive effect when used alone.

The amount of a combination of lacidipine and algosartan required to be effective as antihypertensive may, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation. the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

In general a suitable dose of lacidipine for administration to a human for the treatment of hypertension may be in the range of 0.1 to 10 mg per day, preferably in the range of 1 to 6 mg per day and most preferably in the range 2-6 mg per day. Lacidipine is advantageously administered by oral route once a day.

In general, a suitable dose of algosartan for administration to a human may be in the range of 5 to 120 mg per day, advantageously in the range of 20 to 80 mg per day. Algosartan is advantageously administered by oral route once a day.

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the

sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical formulation. The references hereinafter to formulations refer, unless otherwise stated, to formulations containing either the combination or a component thereof.

A combination of lacidipine and algosartan or a physiologically functional derivative thereof may conveniently be presented as a pharmaceutical formulation in a unitary dosage form. A convenient unitary dosage formulation contains lacidipine in an amount from 1mg to 6 mg and algosartan in an amount from 1O mg to 100 mg.
A particularly convenient unitary dosage formulation contains lacidipine in an amount from 2 mg to 6 mg, more particularly in an amount from 2mg to 4 mg, and algosartan in amount from 20mg to 80 mg.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions,where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation,

containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention provided is a multiple, for example, double or triple, pack comprising at least lacidipine and algosartan or a physiologically functional derivative thereot and an information insert containing directions on the use of the combination of the invention.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or bath, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in

a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, sodium croscarmellose cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored any may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrase and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrase and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or polyethylene glycols.

Topical administration may also be by means of a transdermal iontophoretic device.

Formulations suitable for vaginal administration may be presented as tablets, pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in theart. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonie sterile injection solutions which may contain anti-oxidants, buffers, preservatives and solutes which render the formulation isotonie with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection. immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The pharmaceutical composition of the invention containing the two active ingredients may be prepared according to conventional techniques well known

in the pharmaceutical industry. Thus, for example the lacidipine and algosartan may be admixed together with suitable excipients such as those described above for the formulation of each of the active ingredients separately. Tablets may be prepared, for example by direct compression of such a mixture or using other conventional methods. Bilayer tablets may be prepared according to conventional procedure. Thus, for example, by separately compressing the two blends in a suitable tabletting machine with two filling stations. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

Biological data:

The advantageous profile of antihypertensive activity obtained by the administration of lacidipine with algosartan may be demonstrated in the male spontaneously hypertensive rats.

In this test lacidipine (0.2mg/kg), algosartan (1mg/kg) and a combination of lacidipine (0.2mg/kg) and algosartan (1mg/kg) were administered as a suspension in 0.5% Methocel™I {Hydroxypropyl methyl cellulose) by oral gavage to male spontaneously hypertensive rats.

After dosing, mean blood pressure (MBP) and heart rate (HR) variations were calculated at fixed intervals and expressed as a percentage of pre-drug values. The results obtained three hours after administration of lacidipine and algosartan, alone or in combination, are summarised below:

	Compound	
lacidipine	algosartan	lacidipine

	0.2mg/kg	1mg/kg	0.2mg/kg algosartan 1mg/kg
MBP	-13.8 ± 5.4	-4.5 ± 8.2	-30.5 ± 5.0
HR	1.9 ± 6.4	2.7 ± 17.0	12.6 ± 23.1

The reduction in mean blood pressure with the combination of lacidipine and algosartan was significantly greater than was to be expected and this was also achieved without a significant effect on the heart rate. Duration of action studies also established that the antihypertensive effect of the lacidipine-algosartan combination was clearly longer lasting than the effect induced by lacidipine and algosartan alone.

The compounds of the combination of the present invention may be obtained in a conventional manner.

Lacidipine may be prepared by the method described in British Patent N° 2164336 which is incorporated herein by reference hereto.

Algosartan or a physiologically functional derivative thereof may be prepared by the method described in European Patent N°522222 which is incorporated herein by reference or by known methods described for analogous compounds

For co-administration the lacidipine and algosartan may be formulated in a conventional manner. Thus for example lacidipine may be formulated as described in British Patent N° 2164336 and algosartan may be formulated as described in European Patent N° 522222.

In a preferred aspect of the invention lacidipine and algosartan are formulated in a single pharmaceutical composition.

In order that this aspect of the invention may be more fully understood the following examples are given by way of illustration only.

TABLET FORMULATIONS:

Example 1

The following formulation was prepared by mixing lacidipine granulated containing monohydrate lactose and algosartan spray dried granulate with sorbitol, followed by addition of magnesium stearate and compression.

	mg/tablet
Lacidipine	4
Algosartan	40
Monohydrate Lactose	197
Sodium Hydroxide	3.36
Lysine	12
HPMC	52
Sorbitol	184
Magnesium Stearate	7.5

Example 2

The following formulation was prepared by mixing algosartan spray dried granule with sorbitol and magnesium stearate. Then lacidipine granule was mixed with the remaining magnesium stearate and eventually with sorbitol. The

two blends were separetely compressed in a suitable tabletting machine with two filling stations to produce bilayer tablets.

	mg/tablet
Algosartan	40
Lacidipine	4
HPMC	40
Monohydrate Lactose	197
Sodium Hydroxide	3.36
Lysine	12
HPMC	12
Sorbitol	184.1

The following formulations {Examples 3a-3d) may be prepared by mixing a granulate containing lacidipine, sorbitol and HPMC with algosartan spray dried granulate, sorbitol, followed by addition of magnesium stearate and compression.

Example 3a

	mg/tablet
Algosartan	40
Lacidipine	4
HPMC	52

Sorbitol	116
Sodium Hydroxide	3.36
Lysine	12
Sorbitol	117.64
Magnesium Stearate	5

Example 3b

	mg/tablet
Algosartan	20
Lacidipine	2
HPMC	26
Sorbitol	138
Sodium Hydroxide	1.68
Lysine	6
Sorbitol	151.32
Magnesium Stearate	5

Example3c

	mg/tablet
Algosartan	80
Lacidipine	2
HPMC	44
Sorbitol	138

Sodium Hydroxide	6.72
Lysine	24
Sorbitol	50.28
Magnesium Stearate	5

Example 3d

	mg/tablet
Algosartan	80
Lacidipine	6
HPMC	84
Sorbitol	94
Sodium Hydroxide	6.72
Lysine	24
Sorbitol	50.28
Magnesium Stearate	5

5

Example 4

The following formulation was prepared by granulating algosartan spray dried granule and sorbitol with lacidipine and HPMC followed by addition of sorbitol and magnesium stearate and compression.

10

	mg/tablet
Lacidipine	4
HPMC	40

Sorbitol	88.64
Algosartan	40
Sodium Hydroxide	3.36
Lysine	12
HPMC	12
Sorbitol	295
Magnesium Stearate	5

CLAIMS

1. A combination comprising diethyl (E) -4-(2-((tert-butylcarbonyl)vinyl)phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (lacidipine) and 1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]méthyl]benzimidazole-7-carboxylic (algosartan) or a physiologically functional derivative thereof.

2. A combination according to claim 1 for use in medical therapy.

3. A combination according to claim 1 for use in the treatment and or prophylaxis of hypertension.

4. A combination according to claim 1 wherein the ratio of lacidipine to algosartan is from 1:100 to 1:1 by weight.

5. A method for the treatment of hypertension in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of as claimed in claim 1.

6. A method according to claim 5 wherein the combination is administered as a single combined formulation.

7. A pharmaceutical formulation comprising a combination according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

8. A pharmaceutical formulation according to claim 7 in unit dosage form.

9. The use of lacidipine in the manufacture of a medicament for administration simultaneously or sequentially with algosartan or a physiologically functionally derivative thereof for the treatment and/or prophylaxis of hypertension.

10. A patient pack comprising lacidipine and algosartan or a physiologically functional derivative thereof.

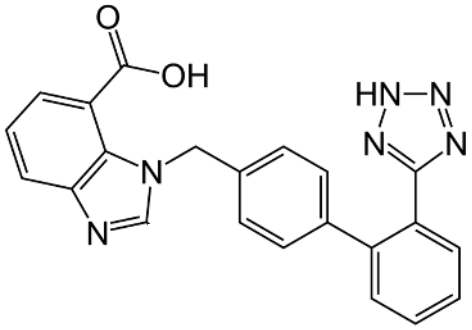
Algo®
(algosartan)
Tablets, 40 mg and 80 mg

Prescribing Information

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ALGO® tablets should be discontinued as soon as possible.
See WARNINGS: Fetal/Neonatal Morbidity and Mortality

DESCRIPTION

ALGO® (algosartan) is a nonpeptide angiotensin II receptor (type AT_1) antagonist. Algosartan is chemically described as 1-[[2'-(1H-tétrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid, having the following formula:



Algosartan is a white slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

ALGO is available as tablets for oral administration, containing 40 mg or 80 mg of algosartan. The tablets contain the following inactive ingredients: sodium hydroxide, lysine, povidone, sorbitol, and magnesium stearate. ALGO tablets are hygroscopic and require protection from moisture.

CLINICAL PHARMACOLOGY

Mechanism of Action
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Algosartan blocks the vasoconstrictor and aldosterone- secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Algosartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because algosartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Algosartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of algosartan on blood pressure.

Pharmacokinetics

General

Following oral administration, peak concentrations (C_{max}) of algosartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of algosartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of algosartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered algosartan are nonlinear over the dose range 40-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Algosartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of algosartan with once daily dosing are about 10-25% of peak plasma concentrations. Algosartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Algosartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of algosartan.

Total plasma clearance of algosartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Distribution

Algosartan is highly bound to plasma proteins (>99.5%), mainly albumin and $_1$ - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for algosartan is approximately 500 liters indicating additional tissue binding.

Special Populations

Pediatric: Algosartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric: The pharmacokinetics of algosartan do not differ between the elderly and those younger than 65 years (see DOSAGE AND ADMINISTRATION).

Gender: Plasma concentrations of algosartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: Renal excretion does not contribute to the clearance of algosartan. Based on modest experience in patients with mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary in patients with decreased renal function. Algosartan is not removed from blood by hemofiltration (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of algosartan are increased, and absolute bioavailability approaches 100% (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Drug Interactions: See PRECAUTIONS, Drug Interactions.

Pharmacodynamics
In normal volunteers, a dose of algosartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of algosartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg algosartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with algosartan 80 mg or algosartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Clinical Trials
The antihypertensive effects of ALGO (algosartan) have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of algosartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95-114 mmHg), 1031 of whom were treated with algosartan. Following once daily administration of algosartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with algosartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with ALGO tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long term studies (without placebo control) the effect of algosartan appeared to be maintained for up to at least one year. The antihypertensive effect of algosartan is not influenced by patient age, gender, weight or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.

In a controlled study, the addition of algosartan to hydrochlorothiazide produced an additional dose-related reduction in blood pressure that was similar in magnitude to the reduction achieved with algosartan monotherapy. Hydrochlorothiazide also had an added blood pressure effect when added to algosartan.

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 40, and 80 mg, the antihypertensive effect of once daily administration of algosartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure

measurements, the 24-hour trough-to-peak ratio for 40-80 mg doses of algosartan was 70-100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with algosartan in controlled trials.

INDICATIONS AND USAGE

ALGO (algosartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

ALGO (algosartan) is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, ALGO (algosartan) tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ALGO tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALGO tablets should be discontinued unless they are considered life- saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

There is no clinical experience with the use of ALGO tablets in pregnant women. No teratogenic effects were observed when algosartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day

[about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) algosartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m basis), administered during late gestation and lactation, were

observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Algosartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m basis, the maximum recommended human dose of algosartan (80 mg/day).

Hypotension in Volume-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with ALGO® tablets. This condition should be corrected prior to administration of ALGO tablets, or treatment should start under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Hepatic Function: As the majority of algosartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. ALGO (algosartan) tablets should be used with caution in these patients.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with ALGO tablets.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long term use of ALGO tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Digoxin: When algosartan was coadministered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing algosartan to avoid possible over- or under-digitalization.

Warfarin: Algosartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs: Coadministration of algosartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Algosartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Algosartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when algosartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are on a mg/m basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD of algosartan. These same doses have been shown to provide average systemic exposures to algosartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any algosartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and *E coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of algosartan.

This dose in the rat resulted in an average systemic exposure (algosartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

It is not known whether algosartan is excreted in human milk, but algosartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients receiving ALGO in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

ALGO (algosartan) has been evaluated for safety in more than 3700 patients, including 1900 treated for over six months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of algosartan (40-160mg) monotherapy for up to 12 weeks, an overall incidence of adverse events similar to that of placebo was observed.

Adverse events occurring at an incidence of 1% or more in patients treated with algosartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in the following table.

	Algosartan *n* = 1455 %	Placebo *n* = 380 %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of 1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea and peripheral edema. Discontinuation of therapy due to adverse events was required in 2.8% of 1455 patients treated with ALGO tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with algosartan in six placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with ALGO monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to ALGO tablets:

Autonomic Nervous System: impotence, increased sweating, flushing; *Body as a Whole:* allergy, fever, leg pain, malaise; *Cardiovascular:* palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG; *CNS*: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia; *Gastrointestinal:* flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders; *Metabolic:* gout, hypercholesterolemia, diabetes mellitus; *Musculoskeletal:* arthritis, arthralgia, leg cramps; *Psychiatric:* anxiety, depression, nervousness; *Resistance Mechanism:* infection, fungal infection, abscess, otitis media; *Respiratory:* asthma, bronchitis, rhinitis, dyspnea, epistaxis; *Skin:* dermatitis, rash, eczema, pruritus; *Urinary:* micturition frequency, cystitis; *Vascular:* cerebrovascular disorder; and *Special Senses:* abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings
In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of ALGO tablets.

Hemoglobin: A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% algosartan patients compared with 0.3% placebo patients. No patients discontinued therapy due to anemia.

Creatinine: A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% algosartan patients compared with 0.3% placebo patients. One algosartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Liver Enzymes: Occasional elevations of liver chemistries occurred in patients treated with algosartan; all marked elevations occurred at a higher frequency with placebo. No algosartan-treated patients discontinued therapy due to abnormal hepatic function.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with ALGO (algosartan) tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Algosartan is not removed by hemodialysis.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. The usual starting dose of ALGO (algosartan) tablets is 40 mg once a day. Blood pressure response is dose related over the range of 40-80 mg (see CLINICAL PHARMACOLOGY:, Clinical Trials).

> **Special Populations:** Patients with depletion of intravascular volume should have the condition corrected or ALGO tablets should be initiated under close medical supervision (see WARNINGS:, Hypotension in Volume-Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see PRECAUTIONS:, General, *Impaired Hepatic Function,* and *Impaired Renal Function*).

Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional blood pressure reduction beyond that achieved with 80 mg ALGO is required, a diuretic may be added.

No initial dosing adjustment is necessary for elderly patients or patients with mild-to-moderate renal impairment. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored.

ALGO tablets may be administered with other antihypertensive agents.

ALGO tablets may be administered with or without food.

HOW SUPPLIED

ALGO (algosartan) is available as white or off-white, uncoated tablets containing algosartan 40 mg or 80 mg. Tablets are marked with the ALGUS PHARMA logo on one side, and on the other side, with either 40 mg, and 80 mg strengths, respectively. Tablets are provided as follows:

ALGO (algosartan) tablets 40 mg are oblong shaped and individually blister-sealed in cartons of 28 tablets as 4 x 7 cards.

ALGO (algosartan) tablets 80 mg are oblong shaped and individually blister-sealed in cartons of 28 tablets as 4 x 7 cards.

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature]. Tablets should not be removed from blisters until immediately before administration.

Rx only

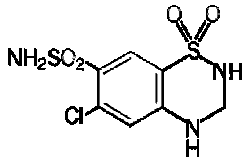
Manufactured by: Algus Pharmaceutical Ltd, UK
Distributed by: Algus Pharmaceutical SA, Spain
Licensed from: Algus Pharmaceutical Ltd, UK

TABLETS

HYDRODIURIL®
(HYDROCHLOROTHIAZIDE)

DESCRIPTION

HydroDIURIL (Hydrochlorothiazide) is a diuretic and antihypertensive. It is the 3,4-dihydro derivative of chlorothiazide. Its chemical name is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



It is a white, or practically white, crystalline powder with a molecular weight of 297.74, which is slightly soluble in water, but freely soluble in sodium hydroxide solution.

HydroDIURIL is supplied as 25 mg and 50 mg tablets for oral use. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C Yellow 6, gelatin, lactose, magnesium stearate, dried corn starch and talc.

CLINICAL PHARMACOLOGY

The mechanism of the antihypertensive effect of thiazides is unknown. HydroDIURIL does not usually affect normal blood pressure.

HydroDIURIL affects the distal renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic efficacy.

HydroDIURIL increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium and bicarbonate.

After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Pharmacokinetics and Metabolism

HydroDIURIL is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS AND USAGE

HydroDIURIL is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.

HydroDIURIL has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.

HydroDIURIL is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Use in Pregnancy. Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Edema during pregnancy may arise from pathologic causes or from the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (see PRECAUTIONS, Pregnancy). Dependent edema in pregnancy, resulting from restriction of venous return by the gravid uterus, is properly treated through elevation of the lower extremities and use of support stockings. Use of diuretics to lower intravascular volume in this instance is illogical and unnecessary. During normal pregnancy there is hypervolemia which is not harmful to the fetus or the mother in the absence of cardiovascular disease. However, it may be associated with edema, rarely generalized edema. If such edema causes discomfort,

increased recumbency will often provide relief. Rarely this edema may cause extreme discomfort which is not relieved by rest. In these instances, a short course of diuretic therapy may provide relief and be appropriate.

CONTRAINDICATIONS

Anuria.
Hypersensitivity to this product or to other sulfonamide-derived drugs.

WARNINGS

Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content.

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Laboratory Tests

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be done at appropriate intervals.

Drug Interactions

When given concurrently the following drugs may interact with thiazide diuretics.

Alcohol, barbiturates, or narcotics - potentiation of orthostatic hypotension may occur.

Antidiabetic drugs - (oral agents and insulin) - dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs - additive effect or potentiation.

Cholestyramine and colestipol resins - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH - intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine) - possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine) - possible increased responsiveness to the muscle relaxant.

Lithium - generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with HydroDIURIL.

Non-steroidal Anti-inflammatory Drugs - In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when HydroDIURIL and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Drug/Laboratory Test Interactions

Thiazides should be discontinued before carrying out tests for parathyroid function (see PRECAUTIONS, General).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 g/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy

Teratogenic Effects - Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use

There are no well-controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients (See DOSAGE AND ADMINISTRATION, Infants and Children.)

ADVERSE REACTIONS

The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity.

Body as a Whole: Weakness.

Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs).

Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia.

Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia.

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance (see PRECAUTIONS), hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis. (See WARNINGS.)

Skin: Erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in the mouse and rat.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response. Use the smallest dosage necessary to achieve the required response.

Adults

For Edema

The usual adult dosage is 25 to 100 mg daily as a single or divided dose. Many patients with edema respond to intermittent therapy, i.e., administration on alternate days or on three to five days each week. With an intermittent schedule, excessive response and the resulting undesirable electrolyte imbalance are less likely to occur.

For Control of Hypertension

The usual initial dose in adults is 25 mg daily given as a single dose. The dose may be increased to 50 mg daily, given as a single or two divided doses. Doses above 50 mg are often associated with marked reductions in serum potassium (see also PRECAUTIONS).

Patients usually do not require doses in excess of 50 mg of hydrochlorothiazide daily when used concomitantly with other antihypertensive agents.

Infants and Children

For Diuresis and For Control of Hypertension

The usual pediatric dosage is 0.5 to 1 mg per pound (1 to 2 mg/kg) per day in single or two divided doses, not to exceed 37.5 mg per day in infants up to 2 years of age or 100 mg per day in children 2 to 12 years of age. In infants less than 6 months of age, doses up to 1.5 mg per pound (3 mg/kg) per day in two divided doses may be required. (See PRECAUTIONS, Pediatric Use.)

HOW SUPPLIED

No. 3263 — Tablets HydroDIURIL, 25 mg, are peach-colored, round, scored, compressed tablets, coded MSD 42 on one side and HydroDIURIL on the other. They are supplied as follows:

NDC 0006-0042-68 bottles of 100

NDC 0006-0042-82 bottles of 1000.

No. 3264 — Tablets HydroDIURIL, 50 mg, are peach-colored, round, scored, compressed tablets, coded MSD 105 on one side and HydroDIURIL on the other. They are supplied as follows:

NDC 0006-0105-68 bottles of 100

NDC 0006-0105-86 bottles of 5000.

Storage

Keep container tightly closed. Protect from light, moisture, freezing, –20°C (–4°F) and store at room temperature, 15-30°C (59-86°F).

Dist. by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued June 1998
Printed in USA

Published in 2000

XP-004367890 D4

COMPARISON OF THE ANTIHYPERTENSIVE EFFECTS OF A FIXED DOSE COMBINATION OF ALGOSARTAN AND HYDROCHLOROTHIAZIDE VERSUS ALGOSARTAN MONOTHERAPY IN MILD TO MODERATE HYPERTENSIVE PATIENTS

Y. ALCOUFIÈRE, L. POMMIER, J. DUVAL, CENTRE HOSPITALIER DE PONDICHERY

To evaluate the antihypertensive effects of a fixed dose combination(FDC) of the angiotensin receptor antagonist algosartan (A) at a dose of 80 mg and hydrochlorothiazide at a dose of 12.5 mg, a study was performed in India comparing the FDC with A 80 mg monotherapy in mild to moderate hypertensive patients who fail to respond adequately to treatment with A 80 mg.

After a one-week screening phase, 781 patients were entered in a 8-week open-label treatment period and were given A 40 mg once daily for a 4-week period. At the end of this period, patients who did not reach target diastolic BP (<90 mmHg) were titrated to A 80 mg for another 4-week period. At the end of this period, 491 patients (309 M/182 F, mean age 55.3 years) who did not reached target diastolic BP (<90 mmHg) were randomized double-bind to either FDC (n=246) or A 80 mg (n=245), both administered once daily, for 8 weeks. Clinic BP was measured at trough (24 hours post-dose) after 4 and 8 weeks of double-blind treatment.

At the end of the double-blind period, patients treated with FDC obtained significant (P<0.001) additional systolic/diastolic clinic BP decrements (-5.7/-3.1 mmHg). Most of these additional effects were obtained during the first 4 weeks of treatment. The proportion of patients with normalized BP (SBP <140 mmHg and DBP<90 mmHg) was significantly (P<0.05) greater in the FDC group (41.5%) as compared to the A 80 mg group (26.1%). Similarly, optimal BP control (SBP < 130 mmHg and DBP<85 mmHg) was reached in a significantly greater proportion of patients in the FDC group as compared to A 80 mg group (19.5% vs 9.4% respectively, P<0.05). Both treatments were generally well tolerated and the incidence of adverse events was similar except for diarrhea, which ocurred more frequently in the A group.

Our results indicate that the FDC of algosartan 80 mg and HCTZ 12.5 mg confers significant additional BP reductions compared to continuation of algosartan monotherapy in non-responders. Patients treated with the FDC also had a significant greater BP response rate compared to patients treated with algosartan alone.

m

D5

Algo® HCT

(algosartan and hydrochlorothiazide)
Tablets, 40mg/12.5 mg

80 mg/12.5 mg and 80 mg/25 mg

Prescribing Information

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ALGO® HCT (algosartan/hydrochlorothiazide) tablets should be discontinued as soon as possible (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

DESCRIPTION
ALGO® HCT (algosartan/hydrochlorothiazide) is a combination of algosartan, an orally active angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Algosartan, a nonpeptide molecule, is chemically described as 1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid.

Algosartan is a white to off-white, odorless crystalline powder. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder with a molecular weight of 297.74. It is slightly soluble in water, and freely soluble in sodium hydroxide solution. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

ALGO HCT tablets are formulated for oral administration in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg, and 80 mg/25 mg algosartan and hydrochlorothiazide, respectively. The tablets contain the following inactive ingredients: sodium hydroxide, lysine, povidone, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, maize starch, sodium starch glycolate. As coloring agents, the 40 mg/12.5 mg and 80 mg/12.5 mg tablets contain iron oxide red, and the 80 mg/25 mg tablets contain iron oxide yellow. ALGO HCT tablets are hygroscopic and require protection from moisture.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Algosartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Algosartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because Algosartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Algosartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of algosartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacokinetics

General

Algosartan:

Following oral administration, peak concentrations (C_{max}) of Algosartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of Algosartan, with a reduction in the area under the

plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of algosartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered algosartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Algosartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of algosartan with once daily dosing are about 10-25% of peak plasma concentrations. Algosartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Hydrochlorothiazide:
When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Elimination
Algosartan:
Following either intravenous or oral administration of ^{14}C-labeled algosartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Algosartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of algosartan.

Total plasma clearance of algosartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Hydrochlorothiazide:
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

Distribution
Algosartan:
Algosartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for algosartan is approximately 500 liters, indicating additional tissue binding.

Hydrochlorothiazide:
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations
Pediatric: Algosartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatric: The pharmacokinetics of algosartan do not differ between the elderly and those younger than 65 years (see DOSAGE AND ADMINISTRATION).

Gender: Plasma concentrations of algosartan are generally 2-3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: Renal excretion does not contribute to the clearance of algosartan. Based on modest experience in patients with mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary in patients with decreased renal function. Algosartan is not removed from blood by hemofiltration (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of algosartan are increased, and absolute bioavailability approaches 100% (see PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Drug Interactions: See PRECAUTIONS, Drug Interactions.

Pharmacodynamics

Algosartan:
In normal volunteers, a dose of algosartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of algosartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg algosartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function
(including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with algosartan 80 mg or algosartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Hydrochlorothiazide:
After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical Trials

Algosartan:
The antihypertensive effects of algosartan have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of algosartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95-114 mmHg), 1031 of whom were treated with algosartan. Following once daily administration of algosartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with Algosartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with Algosartan tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long-term studies (without placebo control) the effect of Algosartan appeared to be maintained for up to at least one year. The antihypertensive effect of Algosartan is not influenced by patient age, gender, weight or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of Algosartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40-80 mg doses of Algosartan was 70-100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with Algosartan in controlled trials.

Algosartan & Hydrochlorothiazide:
In controlled clinical trials with over 2500 patients, 1017 patients were exposed to Algosartan (40 to 160 mg) and concomitant hydrochlorothiazide (6.25 to 25 mg). These trials included one factorial trial with combinations of Algosartan (40, 80, 160 mg, or placebo) and hydrochlorothiazide (6.25, 12.5, 25 mg and placebo). Four other studies of at least six months duration allowed add-on of hydrochlorothiazide for patients who either were not adequately controlled on the randomized monotherapy dose or had not achieved adequate response after completing the up-titration of Algosartan.

The combination of Algosartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 16-21/9-11 mmHg for doses between 40/12.5 mg and 80/25 mg, compared to 9-13/7-8 mmHg for Algosartan 40 mg to 80 mg and 4/4 mmHg for hydrochlorothiazide 12.5 mg alone.

In active controlled studies, the addition of 12.5 mg hydrochlorothiazide to titrated doses of Algosartan in patients who did not achieve or maintain adequate response with Algosartan monotherapy further reduced systolic and diastolic blood pressure.

The antihypertensive effect was independent of age or gender.

There was essentially no change in heart rate in patients treated with the combination of Algosartan and hydrochlorothiazide in the placebo controlled trial.

INDICATIONS AND USAGE
ALGO HCT (Algosartan/hydrochlorothiazide) is indicated for the treatment of hypertension.
This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

ALGO HCT (Algosartan/hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, ALGO HCT (Algosartan/hydrochlorothiazide) tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of ALGO HCT tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALGO HCT tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

A developmental toxicity study was performed in rats with Algosartan/hydrochlorothiazide doses of 3.2/1.0, 15/4.7, 50/15.6, and 0/15.6 mg/kg/day. Although the two higher dose combinations appeared to be more toxic (significant decrease in body weight gain) to the dams than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

No teratogenic effects were observed when Algosartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) Algosartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain.
Algosartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of Algosartan (80 mg/day).

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume-Depleted Patients
Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of ALGO HCT. Treatment should be started under close medical supervision (see DOSAGE AND ADMINISTRATION). If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide
Hepatic Impairment: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be given with thiazides (see PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, *Lithium*).

PRECAUTIONS

Serum Electrolytes

Algosartan & Hydrochlorothiazide:

In controlled trials using the Algosartan/hydrochlorothiazide combination treatment, no patientadministered 40/12.5 mg, 80/12.5 mg or 80/25 mg had a decrease in potassium ≥1.4 mEq/L, and no patient experienced hyperkalemia. No discontinuations due to hypokalemia occurred during treatment with the Algosartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of Algosartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide:

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should beperformed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function
Algosartan:
As the majority of Algosartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. ALGO® HCT tablets should therefore be used with caution in these patients.

Impaired Renal Function
Algosartan:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.
Similar results may be anticipated in patients treated with Algosartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Algosartan in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide:
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Information for Patients
Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension: A patient receiving ALGO HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, ALGO HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving ALGO HCT should be told not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing physician.

Drug Interactions
Algosartan:
Digoxin: When Algosartan was coadministered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing Algosartan to avoid possible over- or under-digitalization.

Warfarin: Algosartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs: Coadministration of Algosartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Algosartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Algosartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Hydrochlorothiazide:
When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressure amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with ALGO HCT.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when ALGO HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the
desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Algosartan & Hydrochlorothiazide:
No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of Algosartan and hydrochlorothiazide.

Algosartan:
There was no evidence of carcinogenicity when Algosartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of Algosartan. These same doses have been shown to provide average systemic exposures to Algosartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any Algosartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and *E coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of Algosartan. This dose in the rat resulted in an average systemic exposure (Algosartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Hydrochlorothiazide:
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, in the Mouse Lymphoma Cell (mutagenicity) assay, and in the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

Pregnancy
Pregnancy Categories C (first trimester) and D (second and third trimesters) (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Nursing Mothers
It is not known whether Algosartan is excreted in human milk, but Algosartan was shown to be present in the milk of lactating rats. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
In the controlled clinical trials (n=1017), approximately 20% of patients treated with Algosartan/hydrochlorothiazide were 65 years of age or older, and 5% were 75 years of age or older. No overall differences in effectiveness and safety of Algosartan/hydrochlorothiazide were observed in these patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
ALGO HCT (Algosartan/hydrochlorothiazide) has been evaluated for safety in over 1700 patients, including 716 treated for over six months and 420 for over one year. In clinical trials with ALGO HCT, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with Algosartan and/or hydrochlorothiazide. The overall incidence of adverse experiences reported with the combination was comparable to placebo. Most adverse experiences were mild in intensity and transient in nature and did not require discontinuation of therapy.

Adverse events occurring at an incidence of 2% or more in patients treated with Algosartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

TABLE 1 Adverse Events Occurring in ≥ 2% of Algosartan/Hydrochlorothiazide (HCTZ) Patients*

	Algo/HCTZ (N=414) (%)	Placebo (N=74) (%)	Algo (N=209) (%)	HCTZ (N=121) (%)
Body as a whole				
Fatigue	**3**	**1**	**3**	**3**
Influenza-like symptoms	2	1	2	3
Central/peripheral nervous system				
Dizziness	**5**	**1**	**4**	**6**
Gastrointestinal system				

Diarrhea	**3**	**0**	**5**	**2**
Nausea	**2**	**0**	**1**	**2**
Respiratory system disorder				
Sinusitis	4	3	3	6
Upper respiratory tract infection	**8**	**7**	**7**	**10**

** includes all doses of Algosartan (40-160 mg), hydrochlorothiazide (6.25-25 mg), and combinations thereof*

The following adverse events were reported at a rate less than 2% in patients treated with Algosartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo: back pain, dyspepsia, vomiting, tachycardia, hypokalemia, bronchitis, pharyngitis, rash, hypotension postural, abdominal pain.

Finally, the following adverse events were reported at a rate of 2% or greater in patients treated with Algosartan/hydrochlorothiazide, but were as, or more common in the placebo group: pain, headache, cough, urinary tract infection.

Adverse events occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

In controlled trials (n=1017), 0.3% of patients treated with ALGO HCT 40/12.5 mg, 80/12.5 mg or 80/25 mg discontinued due to orthostatic hypotension, and the incidence of dizziness was 4%, 7%, and 1% respectively.

Algosartan:
Other adverse experiences that have been reported with Algosartan, without regard to causality, are listed below:
Autonomic Nervous System: impotence, increased sweating, flushing;
Body as a Whole: allergy, fever, leg pain, malaise, chest pain;
Cardiovascular: palpitation, dependent edema, angina pectoris, leg edema, abnormal ECG, hypertension, peripheral edema;
CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia;
Gastrointestinal: flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders;
Metabolic: gout, hypercholesterolemia, diabetes mellitus;
Musculoskeletal: arthritis, arthralgia, leg cramps, myalgia;
Psychiatric: anxiety, depression, nervousness;
Resistance Mechanism: infection, fungal infection, abscess, otitis media;
Respiratory: asthma, rhinitis, dyspnea, epistaxis;
Skin: dermatitis, eczema, pruritus;
Urinary: micturition frequency, cystitis;
Vascular: cerebrovascular disorder;
Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

A single case of angioedema was reported (among a total of 3781 patients treated with Algosartan).

Hydrochlorothiazide:
Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:
Body as a whole: weakness;
Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation;
Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia;
Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous
vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions;
Metabolic: hyperglycemia, glycosuria, hyperuricemia;
Musculoskeletal: muscle spasm;
Nervous System/Psychiatric: restlessness;
Renal: renal failure, renal dysfunction, interstitial nephritis;
Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis;
Special Senses: transient blurred vision, xanthopsia.

Clinical Laboratory Findings
In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of ALGO HCT tablets.

Hemoglobin and Hematocrit: Decreases in hemoglobin (≥ 2 g/dL) and hematocrit (≥ 9%) were observed in 1.2% and 0.6% of Algosartan/hydrochlorothiazide patients, respectively, in controlled trials. Changes in hemoglobin and hematocrit were not considered clinically significant and there were no discontinuations due to anemia.

Creatinine, Blood Urea Nitrogen (BUN): Increases in BUN (≥ 11.2 mg/dL) and serum creatinine (≥0.5 mg/dL) were observed in 2.8% and 1.4%, respectively, of patients with essential hypertension treated with ALGO HCT in controlled trials. No patient discontinued treatment with ALGO HCT due to an increase in BUN or creatinine.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. No Algosartan/hydrochlorothiazide treated patients discontinued therapy due to abnormal hepatic function.

Serum Electrolytes: See PRECAUTIONS.

OVERDOSAGE
Algosartan:
Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with Algosartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Algosartan is not removed by hemodialysis.

Hydrochlorothiazide:
The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

DOSAGE AND ADMINISTRATION

The usual starting dose of Algosartan is 40 mg once a day; blood pressure response is dose related over the range of 20-80 mg. Patients with depletion of intravascular volume should have the condition corrected or Algosartan tablets should be initiated under close medical supervision (see WARNINGS, Hypotension in Volume Depleted Patients). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see PRECAUTIONS).

Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.

To minimize dose independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see WARNINGS) of Algosartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose- independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of Algosartan and hydrochlorothiazide will be associated with both sets of dose- independent side effects.

ALGO HCT tablets may be administered with other antihypertensive agents.

ALGO HCT tablets may be administered with or without food.

Replacement Therapy
The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect
ALGO HCT is available as tablets containing either Algosartan 40 mg and hydrochlorothiazide 12.5 mg, or Algosartan 80 mg and hydrochlorothiazide 12.5 mg. A patient whose blood pressure is not adequately controlled with Algosartan monotherapy 80 mg (see above) may be switched to ALGO HCT, Algosartan 80 mg/hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide may be switched to ALGO HCT (Algosartan 80 mg/hydrochlorothiazide 12.5 mg or Algosartan once daily. The clinical response to ALGO HCT should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to 160/25 mg, if necessary.

Patients with Renal Impairment
The usual regimens of therapy with ALGO HCT may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so ALGO HCT is not recommended.

Patients with Hepatic Impairment
ALGO HCT is not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination (see PRECAUTIONS).

HOW SUPPLIED
ALGO HCT (Algosartan/hydrochlorothiazide) is available in two strengths as biconvex two-layered, oblong-shaped, uncoated tablets in three combinations of 40 mg/12.5 mg and 80 mg/12.5 mg
Algosartan and hydrochlorothiazide, respectively. The hydrochlorothiazide layer is red in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets, and all are unmarked. The Algosartan layer for all two strengths is white, but may contain red specks in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets. The Algosartan layer is marked with the ALGUS PHARMA logo.

Tablets are provided as follows:
ALGO HCT tablets 40 mg/12.5 mg are individually blister-sealed in cartons of 30 tablets as 3 x 10 cards .
ALGO HCT tablets 80 mg/12.5 mg are individually blister-sealed in cartons of 30 tablets as 3 x 10 cards .

Storage
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Tablets should not be removed from blisters until immediately before administration.
Rx only

Manufactured by:	Algus Pharmaceutical Ltd, UK
Distributed by:	Algus Pharmaceutical SA, Spain
Licensed from:	Algus Pharmaceutical Ltd, UK

Réponse d'un candidat

Note attribuée à cette copie 16 / 20

QUESTION 1

EP 1 444 444 (EP' 444) est un brevet européen correspondant à l'entrée en phase EP d'une demande PCT.

EP' 444 a été déposé le 6/2/2002 (nous vérifierons cette date car il semble y avoir une incohérence entre la date de dépôt (6/2/2002) et de publication (4/7/2003, soit moins de 18 mois après).

Si la date de dépôt est correcte, EP' 444 expirera au plus tard en 2022 (sous réserve du dépôt CCP, et du paiement des annuités).

EP' 444 désigne la France. Une validation en France était donc possible. Nous vérifierons auprès de l'INPI qu'effectivement le brevet est validé en FR et que les annuités ont été acquittées.

On note qu'aucune priorité n'est revendiquée.

On note également qu'il existe une demande divisionnaire (EP 1 888 000) : on vérifiera son statut.

EP' 444 a été délivré en 2007, aucune opposition selon A99 auprès de l'OEB n'est donc possible. La validité de ce titre doit donc être abordée dans les états de validation.

En FR, sous réserve que les annuités aient été valablement acquittées, le brevet est considéré valide. La validité pourra être remise en cause devant le TGI de Paris (L. 615-17 + D 631-2 CPI + décret).

La validité de la partie FR s'étudie par rapport à l'A 138 CBE (L. 614-12 CPI).

Les revendications qui font foi sont celles dans la langue de procédure (anglais) : L. 614-10 CPI.

(On notera dans la traduction FR de la revendication 3 la traduction de sucrose par saccharose. Nous vérifierons que cette traduction est exacte).

EP' 444 comprend trois revendications de produit (R1 à R3), une revendication de procédé (R4) et une revendication d'utilisation thérapeutique (R5).

Etude de validité selon A 138(1) CBE

- Paragraphes e) et d) : pas d'information – Nous vérifierons ces points.
- Paragraphe c) (support des revendications dans la demande)
  - R1 : support [14] associé à [17] pour la définition de « subtantially amorphous »
  - R2 : support [28]
  - R3 : support uniquement partiel en [29]
    En effet, [29] indiqua « anhydrous lactose and lactose monohydrate » et non « lactose ».
    R3 n'est donc pas supporté par la description. Le propriétaire du brevet pourrait modifier R3 pour remplacer « lactose » par « anhydrous lactose and lactose monohydrate » (R3 « modifiée ») pour rétablir sa conformité. Nous vérifierons que « lactose » n'était pas dans les revendications de la demande déposée.
  - R4 : support [16], des éléments optionnels ayant été supprimés aux alinéas a, e et f de [16].
  - R5 : il n'y a pas de support littéral dans la description. Cependant, nous considérons que la combinaison de [7] et [8] supporte cette revendication.

  → Sous réserve que le terme « lactose » ne soit pas présent dans le texte de la demande déposée, la R3 ne remplit pas les conditions de A 138 c).
- Paragraphe b) : la description nous paraît suffisante pour l'exécution de l'invention. Nous pourrons rediscuter ce fait ensemble.
- Paragraphe a) : brevetabilité, notamment nouveauté et activité inventive (autres points : ok)

Art antérieur opposable

- Date effective de R1, R2, R3 modifiée, R4 et R5 : 6/2/2002
- Arts antérieurs :
  - EP A 522 222 (cité) [5] : merci de nous fournir ce document.
  - Alcoufière et al, 2000 : merci de nous fournir ce document.
  - D1 : demande PCT WO 00/2222 publiée le 20/5/2000 → document opposable à la nouveauté et à l'activité inventive.
  - D2 : ALGO® : nous n'avons pas de date certaine pour ce document (la mention 2001, copyright ne signifie pas qu'il ait été rendu accessible au public en 2001). Nous vérifierons la date de publication de ce document. Pour l'analyse, il sera considéré comme accessible avant le 6/2/2002 (opposabilité pour nouveauté et activité inventive).
  - D3 et D4 : documents publiés en 1998 et 2000 (respectivement) → opposables à la nouveauté + activité inventive.
  - D5 : document publié en décembre 2003 (nous vérifierons l'information que vous nous avez communiquée) → document non opposable.

D'autres arts antérieurs pourront être recherchés afin de remettre en cause la validité de EP' 444.

Analyse de la nouveauté

D1

D1 décrit une combinaison de lacidipine et d'algosartan, et son utilisation pour le traitement de l'hypertension (page 1 lignes 4-9).

D1 décrit notamment des comprimés bicouches (p 10 lignes 5-7).

D1 décrit dans l'exemple 2 l'obtention de tablettes bicouches, une couche comprenant de l'algosartan, du sorbitol (water – soluble diluant, cf. R3 EP' 444) et du sodium hydroxyde (basic agent, cf. [28] EP' 444).

D1 ne décrit pas un comprimé composant de l'algosartan sous forme amorphe à au moins 90 %.

D1 de décrit pas un comprimé comprenant du HCTZ.

Par conséquent, les revendications R1, R2, R3 modifiée, R4 et R5 sont nouvelles au regard de D1.

D2

D2 décrit des comprimés d'algosartan, du sodium hydroxyde (basic agent, cf. [28] EP' 444), de la lysine (basic agent, cf. R2 EP' 444) et du sorbitol (water soluble diluant, cf. R3 EP' 444) : page 1 de D2.

D2 décrit le traitement de l'hypertension avec lesdits comprimés (page 3, 2nd paragraphe de « Clinical Trials »).

D2 décrit l'utilisation combinée d'algorsan et de HCTZ pour traiter l'hypertension (p 3, avant-dernier paragraphe).

D2 ne décrit pas un comprimé bicouche comprenant de l'algosartan dans une couche et du HCTZ dans une autre couche.

D2 ne décrit pas un procédé d'obtention d'un comprimé pharmaceutique bicouche comprenant les étapes de R4.

D2 ne décrit pas l'algosartan sous forme amorphe à moins 90 %.

Les revendications R1, R2, R3 modifiée, R4 et R5 sont donc nouvelles au regard de D2.

D3

D3 décrit l'utilisation de HCTZ comme diurétique ou anti-hypertension (seul ou en combinaison avec d'autres agents anti-hypertension, p1).

D3 décrit un comprimé comprenant du HCTZ et du « dried com starch », décrit [36] d EP' 444 comme un désintégrant.

D3 ne décrit pas un comprimé bicouche comprenant de l'algosartan sous forme amorphe à au moins 90 %.

D3 ne décrit pas un procédé d'obtention d'un comprimé bicouche selon la R4.

Les revendications R1, R2, R3 modifiée, R4 et R5 sont donc nouvelles au regard de D3.

D4

D4 décrit la combinaison de doses fixes d'algosartan et de HCTZ pour traiter l'l'hypertension (titre).

D4 ne décrit pas de comprimé bicouche comprenant l'algosartan et l'HTCZ. A la lecture de D4, il semble au contraire que deux formulations distinctes soient utilisées (« both administered daily », « both treatments »).

D4 ne décrit pas non plus un procédé pour obtenir un comprimé bicouche selon la R4.

Les revendications R1, R2, R3 modifiée, R4 et R5 sont donc nouvelles au regard de D4.

Analyse de l'activité inventive de R1 à R3 modifiée

D1 décrit un comprimé bicouche comprenant de l'algosartan et la lacipidine, pour traiter l'hypertension.

D1 est considéré comme l'art antérieur le plus proche.

Les différences entre la revendication 1 et D1 sont :

1) La présence d'algosartan amorphe à au moins 90 %.
2) La présence dans la seconde couche de HCTZ.

o Différence 1

On peut en premier lieu noter que D1 n'indique pas de forme crystalline ou amorphe. Il est possible que dans le comprimé de D1, l'algosartan soit sous forme amorphe du fait de son procédé d'obtention (spray drying + voir les méthodes pour obtenir de l'algosartan amorphe [23] de EP' 444).

A supposer que l'algosartan de D1 ne soit pas amorphe à plus de 90 %, il n'y a pas d'effet technique associé à cette différence pour les comprimés : cf. EP' 444 « its initial crystal morphology […] tablet formulation obtained »

Cette différence ne peut donc pas apporter d'activité inventive à la R1.

o Différence 2

- Effet technique lié à la présence de HCTZ : il n'y a pas d'exemple démontrant un quelconque effet dans EP' 444. Cependant, D4 rapporte l'effet d'une combinaison d'algosartan et de HCTZ augmente l'effet de l'algosartan.
  Par ailleurs D2 indique que la combinaison HCTZ + algosartan augmente l'effet anti-hypertension en comparaison à leurs effets séparés.
  Il existe donc un effet au moins additif des deux composés.
- Problème technique : améliorer le traitement de l'hypertension. Afin de démontrer une activité inventive de la combinaison de deux éléments, il convient de démontrer un effet synergique inattendu.
  - o En l'espèce, D4 (et D2) induisant l'homme du métier à combiner l'algosartan et HCTZ pour traiter l'hypertension.
  - o De plus, D1 décrit que l'art antérieur induit à associer l'algosartan à d'autres substances actives (p 1 ligne 21).
  - o Enfin, D3 indique que le HCTZ, combiné à d'autres médicaments anti-hypertension en améliore l'effet (p3 ligne 4).

Au vu de ces différentes divulgations, l'homme du métier aurait été induit à remplacer la lacidipine de D1 par du HCTZ, pour attendre un effet au moins additif.

A supposer que le propriétaire du brevet arrivait à démontrer un effet synergique (ce qui parait peu probable au vu des résultats de D5 p 5, décrivant uniquement un effet additif) il est notre opinion qu'aucun effet inattendu n'est associé à la combinaison d'algosartan et de HCTZ.

Par ailleurs, la composition de la couche de HCTZ (matrice de composé désintégrante) est décrite dans D3.

En conclusion, la R1 est dépourvue d'activité inventive au regard de D1, D2, D3 et D4.

R2 et R3 modifiée ajoutent des caractéristiques décrites dans D1, la même conclusion s'applique donc.

Analyse de l'activité inventive de R5

R5 décrit l'utilisation du comprimé de R1 à R3 pour le traitement de l'hypertension.

Le comprimé de R1 à R3 est dépourvu d'activité inventive.

Par ailleurs, tous les documents décrivent l'utilisation du algosartan et/ou HCTZ pour traiter l'hypertension (voir en particulier D4).

En conclusion, l'utilisation du composé de R1 à R3 pour le traitement de l'hypertension est dépourvue d'activité inventive.

Analyse de l'activité inventive de R4

D1 est le seul document à décrire un procédé de production de comprimé. D1 est donc le document de l'art antérieur le plus proche.

Différence : D1 ne décrit pas les étapes spécifiques de séchage par pulvérisation en présence d'une composition comprenant un solubilisant et un retardateur de cristallisation (povidone par exemple [37] EP' 444).

L'effet technique de cette différence est de faciliter les étapes d'humidification et de dissolution pendant le procédé ([21] EP' 444). Nous n'avons pas identifié de résultat expérimental démontrant ce fait dans EP' 444, un temps de mélange de 9,5 minutes est indiqué tableau [65]. Des résultats comparatifs pourront être apportés pour tenter d'informer cet effet.

Le problème technique objectif que l'on cherche à résoudre est de fournir un procédé permettant de faciliter les étapes d'humidification et de dissolution.

Aucun des documents de l'art antérieur ne décrit ni ne suggère cet effet.

La R4 est donc inventive au regard des documents cités.

Si vous apportez des résultats expérimentaux démontrant qu'il n'y a pas d'impact sur les étapes d'humidification et de dissolution, l'activité inventive pourra être remise en cause.

Conclusion

R1 : pas inventive au regard de D1 + D2/D3/D4.

R2 : pas inventive au regard de D1 + D2/D3/D4.

R3 : non valide pour absence de support (A 138 (1) c)

R3 modifiée : pas inventive au regard de D1 + D2/D3/D4.

R4 : nouvelle et inventive (sous réserve d'un effet technique associé aux étapes a et b).

R5 : pas inventive au regard de D1 + D2/D3/D4.

QUESTION 2

Les revendications d'un brevet délivré sont considérées comme valables. En conséquence, nous considèrerons dans un premier temps les revendications R1 à R5 valides, avant de prendre en compte les conclusions de la question 1.

Revendications de produit

GENERICS : le produit fabriqué par GENERICS correspond à Algo®HCT.

Il comprend entre autres :

- algosteran
- HCTZ
- sodium hydroxide = agent basique selon R2
- lysine : agent basique selon R2
- lactoze monohydrate : diluant soluble selon [29]
- sorbitol : diluant soluble selon R3.

Le comprimé comprend deux couches (cf. votre courrier).

Au vu du procédé utilisé par INDAGIEN, il ressort que la première couche comprend de l'algosartan amorphe (le povidone est décrit par EP' 444 comme un cristalliseur permettant de maintenir l'algosartan sous forme amorphe : [23] + [37]). On peut donc supposer que la première couche du comprimé comprend plus de 90 % d'algosartan sous forme amorphe : ce fait pourra être vérifié expérimentalement.

De plus, vous nous indiquez que la seconde couche comprend de l'HCTZ et des excipients utilisés pour préparer des matrices de comprimés désintégrants.

Il ressort que le produit fabriqué par GENERICS reproduit toutes les caractéristiques de la revendication 1 de EP' 444 (dans la mesure où il comprend effectivement plus de 90 % d'algosartan sous forme amorphe).

Par ailleurs :

- la première couche comprend de l'hydroxyde de sodium (i.e., un hydroxyde de métal alcalin, [28] EP' 444) et de la lysine (agent basique selon R2) : les caractéristiques de la R2 sont également toutes reproduites ?
- la première couche comprend également du sorbitol (i.e., un diluant soluble selon R3) comme indiqué dans votre courrier. En conséquence, toutes les caractéristiques de la R3 sont reproduites.

Les actes constituant une contrefaçon pour des revendications de produit sont définis par L. 613-3 a) + L. 615-1.

En l'occurrence, GENERICS est contrefacteur (et sa responsabilité civile est engagée) du fait de la fabrication du produit objet de R1 à R3 de EP' 444. Par contre il n'y a pas encore de commercialisation.

A noter que GENERICS ne bénéficie plus de l'exemption de L. 613-5 d) puisque vous nous indiquez de l'AMM a été obtenue.

Par ailleurs, nous attirons votre attention sur le fait que l'obtention d'une AMM et d'un prix par l'ANSM donne le feu vert réglementaire à la commercialisation. Or, vous devez également vous assurez que votre produit ne rentre pas dans la portée du brevet d'un tiers.

R5 : les revendications d'utilisation thérapeutique sont des revendications de produit. Si vous détenez des boites de médicament comprenant votre produit et une indication de son utilisation (traitement de l'hypertension, ce qui correspond au produit XXX Algo®HCT), cela constituera un acte de contrefaçon.

GENERICS est donc a priori contrefacteur des revendications R1, R2, R3 et R5 de EP' 444 (sous réserve des remarques précédentes).

Selon notre opinion, aucune de ces revendications n'est valide (ce qui n'est pas le cas non plus de R3 modifié)

En conséquence, en cas d'action en contrefaçon contre GENERICS, la validité des revendications R1 à R3 et R5 pourra être remise en cause et les risques de condamnation sont limités.

INDIAGEN

INDIAGEN produit en Inde une première couche du comprimé. L'effet d'un brevet est territorial : une action en Inde ne peut donc être interdite par un brevet FR. Nous vérifierons l'existence d'un brevet équivalent en Inde.

INDIAGEN et GENERICS importent en FR un produit qui ne remplit pas les conditions des revendications R1 à R3 et R5. Aucun ne court le risque selon L. 613-3 a) + L. 615-1 (importation).

Revendication R4 (procédé)

Aucun de GENERICS ni de INDIAGEN ne reproduit l'ensemble des étapes de la revendication 4. Ils ne sont pas considérés contrefacteurs au titres L. 613-3 b) et L. 615-1.

Cependant, une revendication de procédé couvre également le produit directement obtenu par ce procédé (L. 613-2 2°), cf. L. 613-3 c). En l'occurrence, GENERICS produit un produit correspondant à cette définition.

Dès que GENERICS commercialisera ce produit, il pourra être considéré comme contrefacteur de R4. Sa responsabilité civile pourra être engagée (L. 615-1) en tant que fabricant. Nous rappelons que R est a priori valable.

Contrefaçon pour fourniture de moyens ?

GENERICS importe en France (a priori sans le consentement du propriétaire de EP' 444) des granulés d'algosartan amorphes en vue d'obtenir un comprimé objet du brevet. En l'espèce, INDIAGEN réalise une partie du procédé de R4, et GENERICS la seconde (à partir de l'étape c).

GENERICS met en œuvre en France la seconde étape du procédé breveté.

Les éléments obtenus de INDIAGEN peuvent être considérés comme essentiels (au vu notamment de l'impact de la présence d'algosartan amorphe) et ne se trouvent pas couramment dans le commerce.

Pour remplir les conditions de L. 613-4, il reste à déterminer si :

- INDIAGEN livre en France : on peut supposer que oui mais ce point sera à vérifier,
- GENERICS savait que la composition d'Indiagen était destinée ou apte à la reproduction de R4 : on peut également supposer que oui.

INDIAGEN pourrait donc être inquiété au titre de la fourniture de moyen, s'il était démontré qu'effectivement INDIAGEN livre en France.

Conclusion

GENERICS : contrefaçon R1 à R3 / L. 613-3 a) (mais revendications non valides). Idem R5.

INDIAGEN : éventuelle contrefaçon pour fourniture de moyens L. 613-4.

QUESTION 3

Intervention de l'huissier :

- L'huissier a décliné son identité et celle du CPI accompagnant → OK
- A noter que la présence du Conseil du propriétaire du brevet n'est a priori pas problématique, du moment que celui-ci reste indépendant et impartial dans son attitude (à vérifier dans procès-verbal).
- Les référence aux commentaires du CPI pourront être vérifiées dans le procès-verbal : elles doivent être clairement identifiées comme découlant du CPI (et non de l'huissier).
- L'huissier a remis une copie de la requête et de l'ordonnance de saisie :
    - a-t-il présenté une copie du brevet en cause ? → à vérifier dans le procès-verbal. Si non, cela peut constituer un vice et entraîner la nullité de la saisie ?
    - les opérations de saisie ont débuté 10 minutes seulement après l'arrivée de l'huissier : ce temps parait très court pour que M. BALTA puisse prendre connaissance complète de la requête et de l'ordonnance. Ce fait pourra être contesté.
- L'huissier a eu affaire à M. BALTA (directeur de l'une des productions), i.e., une personne a priori habilitée. Aucune contestation ne pourrait a priori être émise.

M. BALTA nous indique avoir fait des déclarations à la demande de l'huissier. Hors un huissier n'est pas habilité à conduire un interrogatoire, mais doit se limiter à effectuer les actions définies dans l'ordonnance. L'utilisation des déclarations de M. BALTA pourra donc être limités (une contestation sera faite en ce sens).

Nous vérifierons donc ce que couvre l'ordonnance :

- quelles sont les revendications invoquées,
- quelles actions pouvait effectuer l'huissier : description, saisie d'échantillons (de quels échantillons parle-t-on ?), saisie de factures, saisie réelle… (cf. L. 615-5 et L. 615-5-2).

Enfin, M. BALTA nous indique que M. DUCHMOLE (le CPI) a lui-même procédé à un prélèvement, avec des ustensiles et contenants qu'il avait lui-même apportés.

Nous rappellerons que le CPI n'est là que pour assister l'huissier lors d'une saisie, et qu'en aucun cas il ne peut agir de son propre chef.

Une contestation sera émise en ce sens.

QUESTION 4

- Sous peine de nullité de la saisie, le propriétaire doit se pourvoir au fond, par voie pénale ou civile, dans un délai de 20 jours ouvrables ou 31 jours civils (L. 615-5 + R. 615-3).
- Par ailleurs, toute mesure de nature à compléter les actes de contrefaçon allégués pourront être ordonnés par le juge (par exemple saisie du dossier d'AMM au siège social de GENERICS, saisie de document décrivant 1) le produit reçu de INDIAGEN et 2) le procédé mis en œuvre par GENERICS sur ce produit…) L. 615-5 + R. 615-4. Le juge pourra également renverser la charge de la preuve (L. 615-5-1) et demander à GENERICS de prouver que le produit obtenu ne découle pas directement du procédé R4.
- En outre, le juge pourrait également ordonner des mesures permettant de prévenir la commercialisation du produit générique par GENERICS selon L. 615-3.

RAPPORT DES EXAMINATEURS

EPREUVE ECRITE N° 2

I - Votre avis sur la validité du brevet européen EP 1 444 444

Etaient attendus des candidats en introduction les éléments suivants :

- Statut du brevet (paiement des annuités, analyse des dates)
- Présentation de l'art antérieur, opposabilité des documents (D1, D2, D3, D4 opposables, D5 non opposable)
- Rappel de l'article 138
- Exceptions à la brevetabilité : la revendication 5 n'est pas considérée comme une méthode de traitement

A – <u>Nouveauté</u>

1. Revendication 1

- Par rapport à D1 : nouveauté oui, différences = principe actif lacidipine vs.HCTZ
- Par rapport à D2, D3 et D4 : nouveauté oui, différence = bicouche

2. Revendication 4

Par rapport à D1 : nouveauté oui, différences = principe actif, retardateur de cristallisation, étapes du procédé

3. Revendication 5 :

Nouveauté oui puisque revendication 1 nouvelle

<u>Conclusion de la nouveauté</u>

B – Activité inventive

1. Revendication 1 : activité inventive, non

Document le plus proche : D1

Différence : principe actif lacidipine vs.HCTZ

D2 et D4 incitent à combiner l'algosartan et l'HCTZ : pas d'activité inventive

2. Revendication 4

Différence supplémentaire : retardateur de cristallisation

Effet technique (voir paragraphe [0022] du brevet) : maintien de la forme amorphe

Pb technique objectif: améliorer la biodisponibilité

Aucun document ne suggère comment résoudre le problème technique objectif.

Activité inventive : oui

3. Revendications 2, 3 et 5 : pas de caractéristique supplémentaire qui ne soit pas dans les docs

Conclusion de la validité

II - Votre avis sur la réalité de la contrefaçon en France et sur les risques auxquels s'exposent les sociétés GENERICS et INDIAGEN

A noter qu'il était attendu que les candidats examinent toutes les revendications quelle que soit leur conclusion quant à leur validité.

A – Matérialité de la contrefaçon

Le produit de GENERIS reproduit la revendication 1.

Le procédé de GENERIS reproduit les étapes (i) d) et (ii) à (vi) de la revendication 4.

Le procédé de INDIAGEN reproduit les étapes (i) a) à c) de la revendication 4.

B – Actes de contrefaçon

Les risques auxquels s'expose la société GENERIS :

- revendication 1 produit : fabrication, détention et commercialisation imminente
- revendication 4 : produit directement obtenu par le procédé
- revendication 5 : contrefaçon par fourniture de moyens quand ce sera commercialisé

Les risques auxquels s'expose la société INDIAGEN :

- revendication 1 : non
- revendication 4 : fourniture de moyens
- revendication 5 : non

Conclusion sur la contrefaçon

III - Votre avis sur la saisie-contrefaçon

Qu'allez-vous vérifier dans le PV ?

- La cohérence des horaires en début de PV
- Que les opérations ne dépassent pas l'ordonnance
- Que c'est bien l'huissier qui menait les opérations
- Que la saisie réelle est prévue dans l'ordonnance
- Que l'huissier a payé ce qu'ils ont prélevé

Quels sont les éléments qui pourraient permettre de contester le procès-verbal et/ou la saisie-contrefaçon

- Si l'huissier n'a pas procédé lui-même aux prélèvements.
- Un temps très court entre arrivée et début des opérations.
- Facture non mise sous pli confidentiel pouvant contenir des infos commerciales confidentielles (le prix de vente par exemple).

IV – Quels sont les prochains événements auxquels doit s'attendre votre client ?

- Une saisie-contrefaçon au siège
- Une saisie-contrefaçon du dossier d'AMM à l'ANSM
- Une assignation en CF (donner le délai)
- Une demande d'interdiction provisoire

Conclusion générale

INSTRUCTIONS AUX CANDIDATS

EPREUVE ORALE

Le choix du secteur technique est effectué par le candidat au moment de l'inscription (mécanique/électricité ou chimie/pharmacie).

Pour cette épreuve, il est remis au candidat le sujet composé soit d'une note décrivant les éléments du contexte à étudier, soit d'une décision de justice à commenter. Il peut être remis également le texte du brevet en cause, les documents de l'art antérieur (en langue française, anglaise ou allemande) et l'objet suspecté d'être contrefaisant ou une description ou une représentation de celui-ci.

L'épreuve orale consiste en un exposé, suivi d'un entretien avec la commission d'examen, sur l'acquisition et l'exploitation d'un brevet en France, notamment sur les aspects techniques, juridiques et/ou contentieux d'un problème de validité, de propriété et/ou de contrefaçon. Lors de l'entretien, des questions concernant la déontologie professionnelle, l'application des conventions européennes ou internationales et des règlements et directives communautaires ainsi que les droits étrangers prévus au règlement de l'examen pourront être posées. Pour la session 2018 les pays sont : Allemagne et Etats-Unis d'Amérique.

Le candidat dispose de 1h30 pour préparer le sujet qu'il traitera devant le jury pendant environ 30 minutes, sans toutefois que cela excède 45 minutes, questions comprises.

Enfin, à la fin de l'épreuve, le candidat ne devra conserver aucun document écrit ou note personnelle, et devra restituer les documents ou objets qui lui ont été éventuellement remis pour analyse.

EXEMPLE DE SUJET

EPREUVE ORALE

Votre Client, Monsieur Germain TOUFRIT directeur de la société CONFIPRESS vient vous exposer la situation dans laquelle sa société se trouve.

CONFIPRESS est spécialisée dans la fabrication et la commercialisation de confitures facilement applicables. En particulier, son produit phare est commercialisé sous la marque CONFIPROPRE. Vous connaissez bien ce produit car vous aviez participé fin 2009 début 2010 à la rédaction d'une demande de brevet qui le couvrait. Cette demande de brevet avait été déposée au nom de M. Germain TOUFRIT car la société CONFIPRESS était en cours de création. Cependant, après la délivrance de ce brevet en France, la société CONFIPRESS avait repris la gestion des annuités de ce brevet via un prestataire de paiement des annuités. M. Germain TOUFRIT vous montre la page de garde et les revendications de ce brevet FR 1000005 (2988888B).

Ce brevet n'avait pas fait l'objet d'une extension à l'étranger car à l'époque, seul le marché français apparaissait pertinent.

La société s'est développée de façon rapide et elle a maintenant des parts de marché importantes en Europe mais aussi aux Etats-Unis, au Canada et commence à trouver des partenaires au Japon.

Elle a reçu le 28 septembre 2018 de l'INPI le courrier annexé et ne sait pas ce qu'il est possible de faire.

Par ailleurs, elle vous informe que depuis 2010 sa formulation a évolué et que sa palette de produits n'est plus limitée à des confitures aux fruits rouges, mais à tout type de confiture. La fabrication est en totalité faite en France dans les usines de CONFIPRESS et le procédé a été maintenu secret.

Récemment, l'un de ses technico-commerciaux, M. JOUMET, a constaté que lorsqu'il ajoutait 5 % en poids de rouge de cochenille à la confiture juste avant la mise en emballage, non seulement la coloration de la confiture était plus lumineuse mais son écoulement était favorisé.

Le 1er octobre 2018, a eu lieu le salon annuel des nouveautés culinaires. La plaquette «CONFIPROPRE nouvelle formule» a été présentée au stand de la Société CONFIPRESS. La plaquette ne mentionne pas la nouvelle composition mais vante les propriétés du nouveau produit : grande facilité de versement, aspect de la confiture plus appétissant, tout type de fruits.

Dans la gazette du salon, diffusée lors du salon, a été reproduite une interview de M. JOUMET. L'extrait de cette gazette mentionne que l'interview a été diffusée sur Radio Matin Pro le 20 septembre 2018.

L’extrait de la gazette du salon vous est remis par votre client.

La Société CONFIPRESS vous informe également que son « nouveau CONFIPROPRE » sera commercialisé avant Noël en France puis courant du premier trimestre 2019 aux Etats-Unis avec un nouveau partenaire et dans les autres pays en utilisant les mêmes circuits commerciaux que pour le produit classique CONFIPROPRE. Le nouveau partenaire pour les Etats-Unis sera non seulement chargé de la distribution mais également de la fabrication pour le territoire des Etats-Unis mais aussi du Canada.

A ce jour, votre client vous confirme qu’aucune information n’a été divulguée sur le procédé de fabrication qui est la clé de la réussite du produit.

A titre confidentiel, M. Germain TOUFRIT vous indique que le procédé n’est pas très compliqué en soit, mais c’est de celui-ci que vient la réussite du produit. La confiture, contrairement à une confiture classique est cuite en ajoutant progressivement le sucre à la compotée de fruits selon un gradient très précis, indépendant du type de fruit puis, la confiture est refroidie brutalement avant d’être versée dans les dispositifs de distribution (type distributeur de mayonnaise ou de sauce tomate). Une fois rempli, le produit subi une stérilisation flash. Avec la nouvelle formulation, le procédé reste inchangé ce qui présente un avantage formidable car il ne sera pas nécessaire de modifier les chaines de fabrication.

Questions

1. Après avoir analysé la situation, vous conseillerez votre Client sur la meilleure façon de protéger les intérêts de sa Société avant le lancement de son nouveau produit.

2. L’an dernier une publicité de lancement d’un produit concurrent a été repérée par la société CONFIPRESS. Cette dernière a réussi à dissuader ce concurrent en lui envoyant une lettre de mise en demeure. M. TOUFRIT suppose que le concurrent a également renoncé pour des problèmes techniques. Il vous demande votre avis sur les chances de succès qu’aurait pu avoir une action en contrefaçon en France sur la base de son brevet français. Vous supposerez que le produit concurrent est identique au produit CONFIPROPRE.

(19) RÉPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication : 2988888
(à n'utiliser que pour les commandes de reproduction)

(21) N° d'enregistrement national: 1000005

(51) Int Cl[8] : *B 01 D 53/32* (2013.01), B 01 D 53/62, C 25 B 9/18

(12) **BREVET D'INVENTION** **B1**

(54) CONFITURE DE FAIBLE VISCOSITE PERMETTANT SON ECOULEMENT ET DISPOSITIF DE DISTRIBUTION CONTENANT LADITE CONFITURE

(22) **Date de dépôt :** 05.01.2010

(30) **Priorité:**

(43) **Date de mise à la disposition du public de la demande :** 08.07.2011 Bulletin 11/27.

(45) **Date de la mise à disposition du public du brevet d'invention :** 25.04.14 Bulletin 14/17.

(56) **Liste des documents cités dans le rapport de recherche :**

Se reporter à la fin du présent fascicule

(60) **Références à d'autres documents nationaux apparentés :**

(71) **Demandeur(s) :** GERMAIN TOUFRIT

(72) **Inventeur(s) :** GERMAIN TOUFRIT

(73) **Titulaire(s) :** GERMAIN TOUFRIT

(74) **Mandataire(s) :** CABINET EQFPRO

REVENDICATIONS

1. Confiture à base de fruits rouge épépinés présentant après refroidissement à 20-25°C une viscosité de 50-75 CPS.

2. Confiture selon la revendication 1, comprenant 45-65% en poids de fruits et 35 à 55% en poids de sucre.

3. Confiture selon la revendication 1 ou 2 qui est dépourvue de conservateurs.

4. Confiture selon l'une quelconque des revendications 1 à 3, caractérisée par le fait qu'elle contient 2 à 20 % de pectine naturelle ajoutée.

5. Confiture selon la revendication 4, caractérisée par le fait que la pectine est de la pectine de pommme.

6. Dispositif de distribution de confiture telle que définie à l'une des revendications 1 à 5.

7. Dispositif selon la revendication 6, caractérisé par le fait que le dispositif est un dispositif de distribution par pression.

8. Utilisation d'un dispositif selon la revendication 7, pour étaler la confiture sans utilisation d'ustensile de cuisine.

N° d'enregistrement national :1000005555 5 N° de publication : 2988888

RAPPORT DE RECHERCHE

articles L.612-14, L.612-17 et R.612-53 à 69 du code de la propriété intellectuelle

OBJET DU RAPPORT DE RECHERCHE

L'I.N.P.I. annexe à chaque brevet un "RAPPORT DE RECHERCHE" citant les éléments de l'état de la technique qui peuvent être pris en considération pour apprécier la brevetabilité de l'invention, au sens des articles L. 611-11 (nouveauté) et L. 611-14 (activité inventive) du code de la propriété intellectuelle. Ce rapport porte sur les revendications du brevet qui définissent l'objet de l'invention et délimitent l'étendue de la protection.

Après délivrance, l'I.N.P.I. peut, à la requête de toute personne intéressée, formuler un "AVIS DOCUMENTAIRE" sur la base des documents cités dans ce rapport de recherche et de tout autre document que le requérant souhaite voir prendre en considération.

CONDITIONS D'ÉTABLISSEMENT DU PRÉSENT RAPPORT DE RECHERCHE

- ☐ Le demandeur a présenté des observations en réponse au rapport de recherche préliminaire.
- ☒ Le demandeur a maintenu les revendications.
- ☐ Le demandeur a modifié les revendications.
- ☐ Le demandeur a modifié la description pour en éliminer les éléments qui n'étaient plus en concordance avec les nouvelles revendications.
- ☐ Les tiers ont présenté des observations après publication du rapport de recherche préliminaire.
- ☐ Un rapport de recherche préliminaire complémentaire a été établi.

DOCUMENTS CITÉS DANS LE PRÉSENT RAPPORT DE RECHERCHE

La répartition des documents entre les rubriques 1, 2 et 3 tient compte, le cas échéant, des revendications déposées en dernier lieu et/ou des observations présentées.

- ☐ Les documents énumérés à la rubrique 1 ci-après sont susceptibles d'être pris en considération pour apprécier la brevetabilité de l'invention.
- ☒ Les documents énumérés à la rubrique 2 ci-après illustrent l'arrière-plan technologique général.
- ☐ Les documents énumérés à la rubrique 3 ci-après ont été cités en cours de procédure, mais leur pertinence dépend de la validité des priorités revendiquées.
- ☐ Aucun document n'a été cité en cours de procédure.

1. ELEMENTS DE L'ETAT DE LA TECHNIQUE SUSCEPTIBLES D'ETRE PRIS EN CONSIDERATION POUR APPRECIER LA BREVETABILITE DE L'INVENTION

NEANT

2. ELEMENTS DE L'ETAT DE LA TECHNIQUE ILLUSTRANT L'ARRIERE-PLAN TECHNOLOGIQUE GENERAL

NEANT

3. ELEMENTS DE L'ETAT DE LA TECHNIQUE DONT LA PERTINENCE DEPEND DE LA VALIDITE DES PRIORITES

NEANT

RÉPUBLIQUE FRANÇAISE

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INDUSTRIELLE

LP : 2C 130 945 9238 2

7920803:843:10:2:TF3

CABINET EQFPRO
8 Rue de l'avenir
75300 PARIS

LETTRE RECOMMANDEE AVEC A.R.

Objet : BREVET

Numéro: 1000005
Déposé(e) le: 5 janvier 2010

DECISION DE CONSTATATION DE DECHEANCE

LE DIRECTEUR GENERAL DE L'INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

VU le code de la propriété intellectuelle et notamment ses articles L.613-22, R.613-46, R.613-47 et R.618-3 ;

VU le titre ci-dessus désigné ;

ATTENDU que les redevances prescrites (3 ème annuité) pour le maintien en vigueur de ce titre n'ont pas été versées en temps utile ou l'ont été à un taux insuffisant ;

PAR CES MOTIFS

DECIDE

ARTICLE UNIQUE: La déchéance des droits attachés au titre ci-dessus désigné est constatée.

Fait à COURBEVOIE, le 28 septembre 2018
Pour le directeur général de l'Institut national
de la propriété industrielle,
la directrice du département des données

Anne DUFOUR

Voir au verso les conditions et délais d'introduction des recours. La redevance de recours en restauration est 156 Euros

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SALON DES NOUVEAUTES CULINAIRES

Du nouveau chez CONFIPRESS

Lors d'une interview donnée sur Radio Matin Pro le 20 septembre 2018, M. JOUMET technico-commercial de la Société CONFIPRESS a présenté en avant-première la nouvelle gamme de produit qui viendra à terme remplacer CONFIPROPRE qui a été leur produit phare depuis 2010.

En 2010, le produit CONFIPROPRE est apparu comme un produit révolutionnaire. Fini, les cuillères qui tombent au fond des pots de confiture, fini les pots de confitures tout collants, fini la cuillère pleine de confiture posée sur la table…. Avec CONFIPROPRE, la confiture se tartine proprement, sans aide.

Après une telle révolution, comment CONFIPRESS va renouveler sa gamme ? C'est ce que nous expliquait M. JOUMET le 20 septembre dernier.

« Vous avez tous testé et aimé notre produit CONFIPROPRE, cependant, avec certains fruits, la confiture ne s'écoulait pas toujours aussi bien que nous l'aurions souhaité, et la confiture au fond du packaging restait souvent non versable. Nous avons donc cherché à améliorer notre produit et tout récemment, nous avons découvert qu'en utilisant une quantité très spécifique de pectine et en ajoutant 5 % en poids de rouge de cochenille dans notre confiture, quelque soit le fruit, nous obtenions des résultats nettement améliorés en terme de couleur et brillance de la confiture, de facilité d'écoulement et de conservation des propriétés d'écoulement au cours du temps.

Avec ces améliorations et un nouveau packaging que vous découvrirez en fin d'année, nous allons donner une seconde vie à nos produits CONFIPROPRE »

ELEMENTS DE REPONSE

Question 1 : *après avoir analysé la situation, vous conseillerez votre Client sur la meilleure façon de protéger les intérêts de sa Société avant le lancement de son nouveau produit.*

1. Modalité recours en restauration : L. 612-16 et R. 613-52 CPI

   Délai : 2 mois/ un an

   Demande présentée au nom du titulaire inscrit : Mr Germain TOUFRIT

   Motivation : erreur du mandataire (demande d'éléments supplémentaires au client)

2. Demandes à déposer :

Eléments importants pour le choix des demandes de brevet possibles :

- Au salon pas de divulgation sur la composition.
- Divulgation par l'inventeur lors d'une interview du 20 septembre avec divulgation de la teneur en cochenille et de la sélection d'une plage spécifique pour la teneur en pectines.
- Le procédé car la production va être faite en dehors de leur établissement donc secret plus difficile à contrôler.
- Contenant ?

Sur la composition :

- Demande USA large dans le délai de grâce : composition comprenant cochenille.
- Autres pays : brevet de composition avec teneur en pectine : invention de sélection si différente de celle divulguée dans la rev. 4 (+ exemples qui seraient divulgués dans la description).
- Demander éléments et exemples complémentaires pour sélection de la plage spécifique de pectine.

Sur le procédé :

- Recommander d'avoir un brevet car secret ne va plus pouvoir être organisé simplement.
- Demander des détails sur le procédé.
- Dépôt rapide aux USA.

Sur le contenant :

- Demander détails supplémentaires.
- Voir si protection par brevet envisageable.
- Possibilité de dépôt complémentaire d'un modèle si caractère esthétique en plus du caractère technique,
- éventuellement lui suggérer de faire aussi un point sur d'éventuels dépôts de marques, notamment à l'internationale, notamment si ses produits de 2ème génération vont être commercialisés sous une nouvelle appellation et remplacer la 1ère génération ? (en bonus…), mais « confipropre » ne paraît pas super distinctif pour une confiture propre, nom utilisable dans toutes les langues, notamment en anglais ?

3. Pertinence de la Titularité du brevet FR : (pourrait aussi être abordée avec la question 2)

- Au nom de la société qui exploite serait plus pertinent.
- Acte de cession à faire et à inscrire au RNB.
- Attention cession à faire postérieurement à la décision de restauration (R. 613-52 CPI).

4. Envisager la concession de licences à son partenaire américain de son (ses) brevet(s), modèle, marque si dépôt aux USA – avantageux fiscalement ? Marquage aux USA…

   Si absence de titres aux USA, faire accord de confidentialité et exploitation du savoir-faire avec son partenaire.

Question 2 : *l'an dernier une publicité de lancement d'un produit concurrent a été repérée par la société CONFIPRESS. Cette dernière a réussi à dissuader ce concurrent en lui envoyant une lettre de mise en demeure. M. TOUFRIT suppose que le concurrent a également renoncé pour des problèmes techniques. Il vous demande votre avis sur les chances de succès qu'aurait pu avoir une action en contrefaçon en France sur la base de son brevet français. Vous supposerez que le produit concurrent est identique au produit CONFIPROPRE.*

1. Faiblesse des revendications :

Revendication 1 : viscosité pas assez précisément identifiée (type de viscosité, méthode de mesure) : clarté ? ou insuffisance de description ?? à évaluer en fonction du reste de la description.

- Si problème de clarté, la détermination de la portée des revendications pourrait conduire à en écarter le produit concurrent.
- Si insuffisance de description, le brevet est nul.

Revendication 6 : que vaut-elle vraiment ? Nouveauté et activité inventive uniquement car la composition est nouvelle et inventive ?

2. Pertinence d'une limitation avant ou pendant l'action si éléments pertinents dans la description.

   Pour la revendication 1 et pour la revendication 6.

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Contact

Christine PERROT

perqua@inpi.fr

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