TENTAMENOPGAVE “VERDEDIGEN VAN EEN OCTROOIAANVRAGE” (B) CHEMIE 2012

Voor een uitvinding van uw cliënt is een Nederlandse octrooiaanvrage, met inroeping van prioriteit, ingediend, welke aanvrage inmiddels is ingeschreven. Onlangs heeft NL Octrooicentrum de schriftelijke opinie bij het onderzoek naar de stand van de techniek afgegeven.

Opdracht

Stel een brief - gericht aan uw cliënt - op, waarin u gemotiveerd aangeeft welke bezwaren aan de thans beschikbare stand van de techniek kunnen worden ontleend en waarbij u - indien u dat mogelijk acht - verdedigbare conclusies voorstelt die uw cliënt de meest brede bescherming voor zijn uitvinding bieden, met een motivering waarom u die conclusies verdedigbaar acht.

Bijlagen

- Octrooiaanvrage
- Document D1: Handbook of Pharmaceutical Sciences, 15e Edition, 2001, page 137
- Document D2: Handbook of Pharmaceutical Sciences, 15e Edition, 2001, page 579
- Schriftelijke opinie van NL Octrooicentrum bij het onderzoek naar de stand van de techniek
- Document D3: European application 0 456 789
- Document D4: European application 1 234 567
- Document D5: European application 0 345 678

De aanvrage van uw client

Prioriteitsdatum: 20 november 2007 (*)

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Publicatiedatum: 21 mei 2009.

(*) U dient er bij het beantwoorden van de opgave van uit te gaan dat de aanvrage zoals ingediend volledig gelijk is aan het prioriteitsdocument.

Combinatiepreparaat van ashratide en einautide.

De uitvinding heeft betrekking op een farmaceutisch preparaat dat ashratide en einautide omvat.

Ashratide en einautide zijn bekende farmaceutische middelen voor het behandelen van ontstekingsziekten zoals reumatoide artritis, systemische lupus erythematosus, ankyloserende spondylitis (ziekte van Bechterew), inflammatoire darmziekten zoals de ziekte van Crohn, colitis ulcerosa, en psoriasis.

Farmaceutische preparaten op basis van ashratide (een in water oplosbaar peptide van ongeveer 35kDa) en het therapeutisch gebruik ervan bij ontstekingsziekten zijn algemeen bekend (zie bijvoorbeeld het Handbook of Pharmaceutical Sciences, 15e Editie, 2001, blz. 137).

Farmaceutische preparaten op basis van einautide (een peptide van ongeveer 65 kDa, dat kan worden geformuleerd als een complex met zink(2+)-ionen en een farmaceutisch aanvaardbaar complexeermiddel zoals histidine) en het therapeutisch gebruik ervan bij ontstekingsziekten zijn ook algemeen bekend (zie bijvoorbeeld het Handbook of Pharmaceutical Sciences, 15e Editie, 2001, blz. 579).

Er is nu gevonden dat het gebruik van een zink(2+)-complex van ashratide en einautide (in een 1:1 stoechiometrische verhouding) een verrassend synergistisch effect geeft bij het behandelen van ontstekingsziekten. In diermodellen voor ontstekingsziekten is gebleken dat dit zinkcomplex van ashratide en einautide tot wel 1000% meer werkzaam is dan vergelijkbare doses van ashratide en einautide alleen (zie de onderstaande voorbeelden).

De uitvinding heeft derhalve in een eerste aspect betrekking op het zink(2+)-complex van ashratide en einautide in een 1:1 stoechiometrische verhouding.

De uitvinding heeft in een verder aspect betrekking op een farmaceutische samenstelling die het zink(2+)-complex van ashratide en einautide en (ten minste) een geschikte farmaceutische drager omvat. Deze farmaceutische samenstelling kan volgens verdere aspecten een formulering voor infusie of injectie (in het bijzonder voor de behandeling van reumatoide artritis), een formulering voor vertraagde afgifte in de darmen (in het bijzonder voor de behandeling van de ziekte van Crohn of colitis ulcerosa) of een preparaat voor toepassing op de huid zoals een creme (in het bijzonder voor de behandeling van psoriasis) zijn.

Om het zink(2+)-complex van ashratide en einautide te bereiden kunnen ashratide en einautide eenvoudig in equimolaire hoeveelheden worden gemengd in een geschikt waterig medium (zoals een farmaceutisch aanvaardbare buffer die geschikt is voor injectie of infusie) waaraan een farmaceutisch aanvaardbaar en in water oplosbaar zinkzout (zoals zinkchloride of zinkacetaat) is toegevoegd. Representatieve hoeveelheden staan vermeld in de onderstaande voorbeelden. Geschikte media zijn bijvoorbeeld fysiologische zoutoplossing, Ringer's oplossing of een farmaceutisch aanvaardbare fosfaat- of acetaatbuffer.

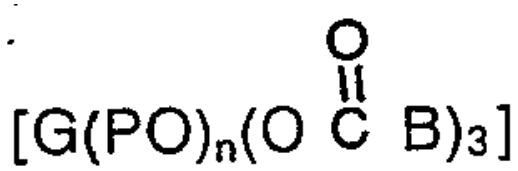
De aldus verkregen oplossing van het complex is direct geschikt voor infusie of injectie. De toegediende doses kunnen liggen tussen 5,0 en 15,0 mg van het complex per kg lichaamsgewicht per dag (zoals ongeveer 10 mg/kg/dag), als een enkele injectie of op geschikte wijze verdeeld over twee of meer injecties per dag. Deze doses zijn vergelijkbaar (op mol-basis) met de doses waarbij ashratide en einautide op dit moment worden gebruikt (dat wil zeggen: ieder afzonderlijk en dus niet als combinatie), waarbij het gebruik van het complex bij deze doses echter leidt tot een synergistisch effect (zie de onderstaande voorbeelden). Deze synergistische werking maakt het eventueel ook mogelijk om lagere doses van het complex te gebruiken en toch een betere of dezelfde werkzaamheid te verkrijgen als kan worden verkregen met de op dit moment gangbare doses van ashratide of einautide alleen. De behandelend geneesheer zal in staat zijn om een geschikt doseringsregime te bepalen.

Voor het behandelen van de ziekte van Crohn of colitis ulcerosa kan het zink(2+)-complex van ashratide en einautide worden toegediend als een oraal preparaat met vertraagde afgifte, dat in staat is om de maag te passeren en daarna het complex in de darmen af te geven. Dergelijke preparaten kunnen op bekende wijze worden samengesteld en bereid, bijvoorbeeld als half-vaste capsules voor vertraagde afgifte op basis van polyol-derivaten die eventueel zijn bekleed met een enterische bekleding, dat wil zeggen een bekleding die zorgt voor passage door

de maag, zonder dat het maagzuur de actieve bestanddelen aantast. Een geschikt voorbeeld hiervan zijn de half-vaste capsules die in EP 0 345 678 worden vermeld, welke 70 tot 80 gewichtsprocent (betrokken op het gewicht van de totale samenstelling) bevatten van de veresterde gealkoxyleerde polyolen die hieronder nader worden beschreven. Dergelijke capsules vormen een verder aspect van de uitvinding.

Geschikte doses van het complex voor het behandelen van de ziekte van Crohn of colitis ulcerosa kunnen door de behandelend geneesheer worden bepaald en kunnen bijvoorbeeld liggen tussen 10 en 50 mg/dag, toegediend als de hiervoor beschreven capsules met 5-10 mg van het complex, die verdeeld over de dag kunnen worden ingenomen.

Het zink(2+)-complex volgens de uitvinding kan ook worden gebruikt voor toepassing op de huid, in het bijzonder het behandelen van psoriasis, en biedt hiermee een lang gewenste behandelingsmogelijkheid voor deze chronische ontstekingsziekte van de huid die maar in beperkte mate kan worden behandeld met gangbare intraveneus toegediende ontstekingsremmers. Hiervoor kan het zink(2+)-complex worden geformuleerd als een crème op basis van de veresterde gealkoxyleerde polyolen die in EP 0 345 678 worden beschreven, dat wil zeggen veresterde gealkoxyleerde polyolen met de algemene formule:



waarin “PO” een C_3-C_6 oxyalkyleen-groep is (verkregen uit een epoxide); “G” een organische groep is die is afgeleid van een alcohol met 2-8 hydroxylgroepen; “B(C=O)O-” een estergroep voorstelt die is afgeleid van een C_8-C_{24} vetzuur met lange keten; en “n” gemiddeld tussen 2 en 18 ligt. De veresterde gealkoxyleerde polyolen die volgens EP 0 345 678 de voorkeur verdienen (zoals de veresterde gealkoxyleerde polyolen op basis van glycerol, propyleenoxide en palmitinezuur met een waarde voor n van ongeveer 10 die in Voorbeeld 1 van EP 0 345 678 worden beschreven), verdienen ook de voorkeur voor gebruik bij de onderhavige uitvinding.

Een dergelijke crème (die een verder aspect van de uitvinding vormt) heeft de volgende samenstelling:

Complex:	14-20 mg per ml van de crème
Water of farmaceutische buffer:	40-50 gewichtsprocent van de samenstelling
Veresterde gealkoxyleerde polyol(en):	50-60 gewichtsprocent van de samenstelling

Deze crème heeft verder het voordeel dat deze lang op de huid aanwezig blijft, en kan daarom bijvoorbeeld elke 4 uur, 6 uur, 8 uur of 12 uur op de aangetaste delen van de huid worden aangebracht. De crème heeft verder een hydraterende werking en vormt bovendien, door zijn uitstekende film-vormende eigenschappen, een beschermende laag op de huid.

De crème met het complex kan worden bereid door het oplossen van de gewenste hoeveelheid ashratide en polyol in water of een farmaceutische buffer waaraan een farmaceutisch aanvaardbaar en in water oplosbaar zinkzout is toegevoegd onder stevig roeren en bij een temperatuur van 50 tot 60°C. Vervolgens wordt de gewenste equimolaire hoeveelheid einautide toegevoegd en de massa afgekoeld tot kamertemperatuur zodat een viskeus en uitsmeerbaar preparaat wordt verkregen.

<u>Voorbeeld 1: Bereiden van een oplossing voor injectie of infusie met 10 mg complex per ml.</u>

350 mg ashratide werd onder roeren bij kamertemperatuur opgelost in 100 ml van een farmaceutische fosfaatbuffer met daarin 0,2M zink-acetaat. Daarna werd 650 mg einautide toegevoegd waarna nog 15 minuten werd geroerd totdat de einautide volledig was opgelost.

De aldus verkregen oplossing van het complex is geschikt voor infusie of injectie.

<u>Voorbeeld 2: Gebruik van een oplossing van het complex voor het behandelen van reuma.</u>

De oplossing van het complex uit Voorbeeld 1 (10 mg complex/ml) werd getest in het Kollias-muismodel voor reuma (Kollias, 2003). In totaal werd 10 mg/kg lichaamsgewicht/dag toegediend, verdeeld over 2 injecties per dag. Zoals gebruikelijk in dit diermodel werden de dieren na 5 dagen onderzocht op de symptomen van reuma. Hiertoe werden de verschillende ziekte-scores bepaald, zoals gebruikelijk voor dit diermodel.

Om aan te tonen dat het complex een synergistische werking heeft werd de verbetering van de ziekte-scores in dit model vergeleken met: (i) een 3,5 mg/ml oplossing van ashratide in dezelfde acetaatbuffer (tweemaal daags toegediend in een totale hoeveelheid van 7 mg/kg/dag); (ii) een oplossing van het zink(2+)/histidine-complex van einautide (6,5 mg einautide/ml) in

dezelfde acetaatbuffer (tweemaal daags toegediend in een totale hoeveelheid van 13 mg/kg/dag); en (iii) het toedienen van zowel ashratide (3,5 mg/kg/dag, verdeeld over twee injecties per dag) en einautide (6,5 mg/kg/dag als het zink(2+)/histidine-complex, ook verdeeld over 2 injecties per dag).

In alle gevallen leidde het gebruik van het complex tot een hogere verbetering (800-1000% meer) van de ziekte-scores dan het gebruik van de referenties (i), (ii) of (iii).

Voorbeeld 3: Bereiden van een crème met 14-20 mg/ml van het zinkcomplex.

Om een crème met het zink(2+)-complex te bereiden werden eerst ashratide (500-700 mg) en de veresterde gealkoxyleerde polyol volgens Voorbeeld 1 van EP 0 345 678 (55 gew. %, betrokken op het totale gewicht van de samenstelling) opgelost in 100ml van een farmaceutische fosfaatbuffer met daarin 0,2M zinkacetaat, onder stevig roeren en bij een temperatuur van 50 tot 60°C. Daarna werd een equimolaire hoeveelheid einautide toegevoegd (900-1300 mg). Na afkoelen tot kamertemperatuur werd een viskeus en uitsmeerbaar preparaat verkregen dat direct als crème op de huid kan worden toegepast.

Het is gebleken dat de hoeveelheid van de veresterde gealkoxyleerde polyol hierbij tussen 50 en 60 gewichtsprocent van de samenstelling moet liggen: een grotere hoeveelheid polyol leidt tot een samenstelling die te viskeus is om als crème te worden toegepast, en bij lagere hoeveelheden van de polyol lost de hiervoor genoemde hoeveelheid einautide niet volledig op in de oplossing van de ashratide met de polyol.

Voorbeeld 4: Gebruik van de crème voor het behandelen van psoriasis.

De in Voorbeeld 3 beschreven crème (op basis van 55 gew.% polyol) werd bereid met verschillende hoeveelheden van het zinkcomplex, en tweemaal daags toegepast op de huid van een muis met psoriasis (in een standaard muismodel voor psoriasis, zie Zenz en Wagner, 2005).

Na 5 dagen werd de verbetering van de psoriasis-scores bepaald, op de voor dit diermodel gangbare wijze.

Ter vergelijking werden crèmes op basis van hetzelfde polyol met ashratide of het zink/histidine complex van einautide getest. De proef met 14,0 mg/ml ashratide diende daarbij als de referentiewaarde.

Dit is een hoeveelheid die op mol-basis overeenkomt met de hoogste hoeveelheid van het complex die werd gebruikt (20 mg van het complex per ml), en ligt ook dicht bij de maximale hoeveelheid die in de literatuur wordt vermeld (zie de Handbook of Pharmaceutical Sciences, 15e Ed, 2001, blz. 137).

Het was door de beperkte oplosbaarheid van de einautide (maximaal 6-7 mg/ml in waterige media) niet mogelijk om een crème te maken met een equivalente hoeveelheid einautide (hetgeen een crème met 26 mg/ml einautide zou zijn geweest). In plaats hiervan werd daarom een crème op basis van een verzadigde einautide oplossing (d.w.z. met 6-7 mg einautide per ml) gebruikt (afzonderlijk en in combinatie met de crème op basis van ashratide – zie Tabel 1). Dit gaf echter minder of hooguit dezelfde verbetering van de psoriasis-scores als de als referentie gebruikte crème met 14 mg/ml ashratide alleen.

De verkregen scores zijn in de onderstaande Tabel 1 weergegeven als percentage ten opzichte van de verbetering die verkregen werd met de referentie (crème met 14 mg ashratide per ml).

Zoals blijkt uit Tabel 1 geven de crèmes met lage concentraties van het complex (10-12mg/ml) ongeveer dezelfde verbetering in psoriasis-score als de combinatiebehandeling met een crème met een hoge concentratie ashratide en een crème met de maximaal mogelijke concentratie einautide. Zelfs al wijst dit op enige synergie, het effect is beperkt omdat de dosering kennelijk niet hoog genoeg is. Pas bij hogere concentraties van het complex treedt een aanzienlijke verbetering op.

TABEL 1

Gebruikte crème	**Toegepast**	**Verbetering t.o.v. referentiewaarde**
Crème met 14 mg/ml ashratide	2 x daags	*[Referentiewaarde]*
Crème op basis van verzadigde oplossing van het zink/histidine complex van einautide	2 x daags	*[Slechter dan de referentiewaarde]*
Crème met 14 mg/ml ashratide; **samen met:** crème op basis van verzadigde oplossing van het zink/histidine complex van einautide	2 x daags 2 x daags	+ 15 %
Crème met 10,0 mg/ml complex	2 x daags	+ 1 %
Crème met 12,0 mg/ml complex	2 x daags	+ 15 %
Crème met 14,0 mg/ml complex	2 x daags	+ 200 %
Crème met 16,0 mg/ml complex	2 x daags	+ 245 %
Crème met 18,0 mg/ml complex	2 x daags	+ 255 %
Crème met 20,0 mg/ml complex	2 x daags	+ 250 %

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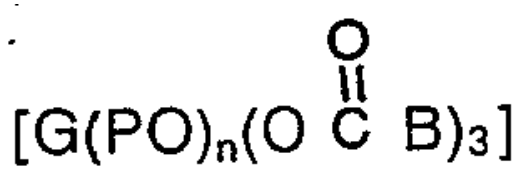
Conclusies:

1. Het zink(2+)-complex van ashratide en einautide in een 1:1 stoechiometrische verhouding
2. Farmaceutische samenstelling die het zink(2+)-complex van ashratide en einautide en een geschikte farmaceutische drager omvat.
3. Farmaceutische samenstelling volgens conclusie 2, die een formulering voor infusie of injectie is.
4. Farmaceutische samenstelling volgens conclusie 3, voor de behandeling van reumatoide artritis.
5. Farmaceutische samenstelling volgens conclusie 2, die een formulering voor vertraagde afgifte in de darmen is.
6. Farmaceutische samenstelling voor vertraagde afgifte van het zink(2+)-complex van ashratide en einautide in de darmen volgens conclusie 5, die half-vaste capsules op basis van veresterde gealkoxyleerde polyolen omvat met de algemene formule:



waarin “PO” een C_3-C_6 oxyalkyleen-groep is (verkregen uit een epoxide); “G” een organische groep is die is afgeleid van een alcohol met 2-8 hydroxylgroepen; “B(C=O)O-” een ester group voorstelt die is afgeleid van een C_8-C_{24} vetzuur met lange keten; en “n” gemiddeld tussen 2 en 18 ligt.

7. Farmaceutische samenstelling volgens conclusie 5 of 6, voor de behandeling van de ziekte van Crohn of colitis ulcerosa.
8. Farmaceutische samenstelling volgens conclusie 2, die een preparaat voor toepassing op de huid is.
9. Farmaceutische samenstelling volgens conclusie 8, voor de behandeling van psoriasis.

Schriftelijke opinie van NL Octrooicentrum bij het onderzoek naar de stand van de techniek:

D3 Europese aanvrage 0 456 789
D4 Europese aanvrage 1 234 567
D5 Europese aanvrage 0 345 678

Uit D3 is bekend het zink(2+)-complex van ashratide en einautide in een 1:1 stoechiometrische verhouding, een oplossing voor infusie of injectie omvattende dit complex voor de behandeling van reumatoide artritis en half-vaste capsules voor de vertraagde afgifte van dit complex in de darmen op basis van veresterde gealkoxyleerde polyolen zoals beschreven in D5 voor de behandeling van de ziekte van Crohn of colitis ulcerosa.
Conclusies 1-7 zijn daarom niet nieuw in het licht van D3.

Uit D4 is bekend het zink(2+)-complex van ashratide en einautide in een 1:1 stoechiometrische verhouding en een spray omvattende dit complex voor de behandeling van psoriasis. Conclusies 1, 2, 8 en 9 zijn daarom niet nieuw in het licht van D4.

Document D1: Handbook of Pharmaceutical Sciences, 15e Edition, 2001, page 137.

ASHRATIDE

Description of compound, indications and uses.

Ashratide is a small (35 kDa) peptide that can be used for the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, colitis ulcerosa and psoriasis.

Ashratide can be formulated for infusion, injection, oral or topical administration (see below).

Formulation:

Ashratide is a water-soluble peptide that can be formulated in concentrations up to 40 mg/ml in any commonly used pharmaceutically acceptable aqueous medium, such as a physiological saline solution, Ringer's solution or a pharmaceutically acceptable phosphate or acetate buffer. The medium can also contain commonly used pharmaceutically acceptable complexing agents such as histidine; however, this is not required to achieve the desired pharmaceutical concentrations.

Usual concentrations of ashratide in solutions for injection or infusion are around 5.0 mg/ml to 10 mg/ml in a suitable pharmaceutically acceptable medium. Effective amounts commonly administered through infusion or injection are between 3 and 15 mg/kg body weight/day, such as between 7 and 10 mg/kg body weight/day, for example as one or two injections per day.

For topical administration to the skin, suitable water-based solutions, creams or ointments comprising between 5 mg/ml and 15 mg/ml of ashratide can be used. Ingredients known *per se*

for formulating creams and ointments for topical administration can be used (in usual amounts), such as polyols and polyol-derivatives (see however the warning below).

Warnings:

Ashratide is acid-sensitive. Thus, for oral administration for the treatment of Crohn's disease or colitis ulcerosa, ashratide needs to be formulated as an oral delayed release formulation capable of passing through the stomach. Ingredients known *per se* for formulating oral delayed release formulations may be used (in usual amounts), such as polyols and polyol-derivatives (see however the warning below).

Some polyols and polyol-derivatives may not be compatible with ashratide, due to the formation of large-scale insoluble aggregates. Thus, before formulating ashratide with any specific polyol or polyol-derivative, the compatibility of ashratide and the intended polyol or polyol-derivative should be tested, simply by mixing the same in the intended aqueous buffer at the desired concentrations.

Document D2: Handbook of Pharmaceutical Sciences, 15e Edition, 2001, page 579.

EINAUTIDE

Description of compound, indications and uses.

Einautide is a 65 kDa peptide that can be used for the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, colitis ulcerosa and psoriasis.

Einautide can be formulated as a complex with zinc (2+)-ions and histidine for infusion, injection, oral or topical administration (see below).

Formulation:

Einautide by itself is essentially insoluble in water or aqueous media. However, einautide can form a complex with zinc(2+)-ions and a pharmaceutically acceptable complexing agent such as histidine. This complex has a limited degree of solubility in aqueous pharmaceutical media (limited to about 6-7 mg/ml – see below).

Accordingly, to prepare aqueous pharmaceutical formulations of einautide, einautide must be dissolved in an aqueous medium that contains a suitable amount of histidine (at least two times the molar amount of einautide used) and a suitable concentration (in excess of the molar amount of einautide used) of a pharmaceutically acceptable zinc(2+)-salt, such as zinc-chloride or zinc-acetate. Any commonly used pharmaceutically acceptable aqueous medium (such as a physiological saline solution, Ringer's solution or a pharmaceutically acceptable phosphate or acetate buffer) can be used.

When formulated in this manner as a complex with zinc(2+) and histidine, einautide can be dissolved in amounts up to 6-7 mg/ml einautide/ml. Such solutions of the zinc(2+)/histidine-complex of einautide can be used for injection or infusion. Amounts commonly used for

administration by infusion or injection are between 12.5 and 25 mg/kg body weight/day, for example as one or two injections per day.

For topical administration to the skin, suitable water-based solutions, creams or ointments comprising of the zinc(2+)/histidine-complex of einautide can be used. Ingredients known *per se* for formulating creams and ointments for topical administration can be used (in usual amounts), such as polyols and polyol-derivatives. Again, the amount of einautide in such topical formulations will be limited by the aforementioned restricted solubility of the complex in aqueous media.

Warnings:

Einautide has limited solubility in aqueous media. As mentioned above, einautide can be dissolved in aqueous media in amounts up to 6 to 7 mg einautide/ml as a complex with zinc(2+) and histidine.

Einautide is essentially not capable passing through epidermal layers such as the skin or wall of the gastrointestinal tract. Accordingly, oral administration of einautide can only be used for the treatment of inflammatory disorders of the gastrointestinal tract, and not for the treatment of rheumatoid arthritis or systemic lupus erythematosus (for this, administration by injection or infusion must be used). Administration of the complex by injection or infusion cannot be used for the treatment of psoriasis (for this, topical application to the skin is required).

Document D3: European application 0 456 789

Title: Compositions for treating inflammatory disorders

Applicant: Berlin Gesellschaft fur Technologische Forschung, GmbH,

Inventors: Baumann, P.; Schulze, K.

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Designated Contracting States: BE, DE, FR, GB, IT, NL

The present invention relates to compositions for the treatment of inflammatory disorders.

The invention is based on the finding that the complex of ashratide (see: Handbook of Pharmaceutical Sciences, 15th Ed., 2001, page 137) and einautide (see: Handbook of Pharmaceutical Sciences, 15th Ed., 2001, page 579) with zinc(2+)-ions has a synergistic effect when used for the treatment of inflammatory disorders.

For example, in two specific but non-limiting aspects, it has been found that the complex zinc(2+)-complex of ashratide and einautide has:

- a synergistic effect on the treatment of rheumatoid arthritis or lupus erythemathosus when administered by injection or infusion (as further described herein); and
- a synergistic effect on inflammatory disorders of the intestinal tract when administered by means of a suitable oral delayed release formulation (as further described herein).

When tested in representative animal models, the synergistic effect provided by the use of the zinc(2+)-complex was up to 1000 % more than the therapeutic effect provided by the use of ashratide alone, of einautide alone, or of ashratide and einautide in combination (see the Examples below).

Thus, in a first aspect, the present invention relates to the zinc(2+)-complex of ashratide and einautide (in equimolar amounts).

In a further non-limiting aspect, the invention relates to such a complex for use in the treatment of inflammatory disorders such as, without limitation, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease or colitis ulcerosa.

In another non-limiting aspect, the invention relates to a pharmaceutical composition that comprises the zinc(2+)-complex of ashratide and einautide, and optionally one or more pharmaceutically acceptable carriers or excipients.

The invention also relates to such a formulation for use in the treatment of inflammatory disorders such as, without limitation, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease or colitis ulcerosa.

In one specific, but again non-limiting aspect, the above pharmaceutical composition is a solution for infusion or injection; and in particular such a solution for infusion or injection for use in the treatment of rheumatoid arthritis, systemic lupus erythematosus or other inflammatory diseases that can be treated by administering the complex by infusion or injection.

In another specific, but again non-limiting aspect, the pharmaceutical composition is an oral delayed release formulation; and in particular such an oral delayed release formulation for use in the treatment of Crohn's disease, colitis ulcerosa or other inflammatory diseases of the intestinal tract.

Interestingly, during the research leading up to the present invention, it was found that administration of the zinc(2+)-complex of ashratide and einautide by injection or infusion (in amounts far exceeding the amounts that were found to be effective in the treatment of rheumatoid arthritis) had no noticeable effect in an representative animal model of Crohn's disease (data not shown). Without being limited to any explanation or hypothesis, we believe this is due to the known fact that the einautide component of the complex has a very limited ability to pass through epidermal layers, which means that einautide has to be applied to the intestinal tract in order to be effective against inflammatory disorders of the intestinal tract (see for example the Handbook of Pharmaceutical Sciences, 15th Ed. (2001), page 579).

Conversely, and we think possibly again due to the known fact that einautide cannot cross epidermal layers such as the wall of the gastrointestinal tract and thus cannot pass from the intestinal tract into the circulation/bloodstream, we have found that oral delayed release administration of the zinc(2+)-complex in amounts that far exceeded the amounts that were

found to be effective in an animal model for Crohn's disease, had not noticeable effect in a representative animal model of rheumatoid arthritis or lupus erythematosus (data not shown).

Formulations for injection or infusion for the treatment of rheumatoid arthritis and lupus erythemathosus.

In order to prepare solutions for injection or infusion of the zinc(2+)-complex, einautide can be dissolved in a solution of an equimolar amount of ashratide in a suitable pharmaceutical medium (such as a physiological saline solution, Ringer's solution or a pharmaceutically acceptable phosphate or acetate buffer) in the presence of a suitable excess concentration (for example 0.1 M) of a pharmaceutically acceptable zinc(2+)-salt, such as zinc-chloride or zinc-acetate.

One would expect that that the concentration of the complex is limited by the solubility of the einautide, which is known to have a maximum solubility of about 7 mg/ml when complexed with zinc(2+) in the presence of a complexing agent such as histidine (see the Handbook of Pharmaceutical Sciences, 15th Ed., 2001, page 579). So, using 650 mg einautide and 350 mg ashratide per 100 ml of the zinc(2+)-containing medium, the highest concentration of the zinc(2+)-complex in solution that can be achieved is 10 mg/ml.

Also, attempts to increase the solubility of the ashratide/einautide/zinc(2+)-complex by adding histidine (as a complexing agent) failed. In fact, it was found that when histidine was added to a solution of the ashratide/einautide/zinc(2+)-complex, that the synergistic effect of the complex was lost (see Example 1 below). Without being limited to any explanation or hypothesis, it is assumed that when histidine is added to a solution of the ashratide/einautide-complex, it replaces the ashratide in the complex, so that the complex is destroyed and the synergistic effect is lost.

For the treatment of rheumatoid arthritis or lupus erythematosus, the solution of the ashratide/einautide/zinc(2+)-complex can be administered by infusion or injection in amounts of between 5 and 15 mg of the complex/kg body weight/day, for example divided over one, two or three injections per day. When considered on a molar basis, these amounts of the complex (which provide the synergistic effect) are roughly comparable to 3-15 mg ashratide/kg/day and to 12.5-25 einautide mg/kg/day, respectively, which are the amounts that are mentioned in the prior art for the use of ashratide and einautide alone (see the aforementioned pages from the Handbook of Pharmaceutical Sciences). Of course, as will be clear to the skilled person, and depending on

the disease to be treated, the synergistic effect provided by the complex of the invention may also allow the treating physician to administer correspondingly lower doses of the complex and still obtain a therapeutic effect which is better than or comparable to the use of ashratide or einautide alone.

Formulations for oral administration for the treatment of Crohn's disease and colitis ulcerosa.

For oral administration, the zinc(2+)-complex of ashratide and einautide must be administered in the form of an oral delayed release formulation (i.e. a formulation that allows the complex to pass through the stomach and then releases the complex in the intestines), as it is known that ashratide is acid-sensitive (see: Handbook of Pharmaceutical Sciences, 15th Ed., 2001, page 137).

Generally, any suitable oral delayed release formulation known for the delivery of ashratide to the intestines can also be used for administration of the zinc(2+)-complex. As mentioned in the Handbook of Pharmaceutical Sciences, 15th Ed., 2001, page 137, such delayed release formulations may for example be based on polyols or polyol-derivatives (provided these are sufficiently compatible with ashratide – see the warning given in the aforementioned Handbook).

A non-limiting example of such a suitable delayed release formulation is the capsule formulation for delayed release based on esterified alkoxylated polyols that is described in the European application 0 345 678.

For example, to prepare such capsules, 75 % by weight (calculated based on the weight of the final composition) of the esterified alkokylated polyol described in Example 1 of EP 0 345 678 may be slowly added, under vigourous stirring so as to obtain a homogeneous solution, to 25 % by weight (again calculated based on the weight of the final composition) of a solution of 350 mg ashratide in 100 ml physiological saline solution containing 0.1 M zinc-chloride, which is kept at a temperature of around 65ºC. Then 650 mg einautide is added. Stirring is continued for another 30 minutes (to allow the complex to form) and is then stopped, after which the solution is allowed to cool to around 50ºC, whereupon a highly viscous mass is obtained that can be fed to a capsule-shaping machine (operating at a temperature of about 50ºC) to form the solution into capsules with a volume of about 1.0 ml per capsule that contain about 5 mg of the complex.

After further cooling to below 40ºC, these capsules become semi-solid, and if desired can then be further coated with an enteric coating layer known per se.

For the treatment of Crohn's disease or colitis ulcerosa, for example between one and three of these capsules can be taken once, twice or three times per day (dosage regimen to be determined by the treating physician), which gives a total daily dose between 5 and 45 mg.

Example 1: treatment of rheumatoid arthritis.

The zinc(2+)-complex of ashratide and einautide was tested in a standard mouse model for rheumatoid arthritis (Kollias, 2003). The complex, ashratide alone (reference), einautide alone (as a zinc(2+)complex with histidine), and a combination treatment with both ashratide and einautide (again as a zinc(2+)complex with histidine) were administered by injection twice per day (in amounts corresponding to equimolar amounts of each active substance, i.e. 10 mg/kg/dag of the complex, 7.0 mg/kg/day ashratide, and 13.0 mg/kg/dag einautide). The improvements of the arthritic scores were determined in the standard manner after 5 days of treatment and were expressed as a percentage over the improvement of the arthritic scores that was obtained with the reference (ashratide alone). The results are shown in Table A below:

TABLE A

Treatment	**Dose administered (divided over two injections per day)**	**Improvement vs reference**
Ashratide (3.5 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride)	7.0 mg per kg body weight per day.	*[reference value]*
Einautide (7 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride and 0.1 M histidine)	13.0 mg per kg body weight per day.	+ 10 %
ashratide (3.5 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride): *in combination with:* einautide (7 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride and 0.1 M histidine):	ashratide: 3.5 mg per kg body weight per day; *and:* einautide: 6.5 mg per kg body weight per day.	+ 5 %
Complex (10 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride)	10.0 mg per kg body weight per day.	+ 875 %

By comparison, if the complex (10.0 mg per kg body weight per day) was formulated and administered in a 10 mg/ml in a physiological saline solution containing 0.1 M zinc-chloride and 0.1 M histidine, the improvement of the arthritic score compared to the reference (ashratide alone, see the table above) was only 7%, which shows that the presence of histidine likely degrades the complex and so removes the synergistic effect.

Example 2: treatment of Crohn's disease.

The zinc(2+)-complex of ashratide and einautide was tested in a standard mouse model for Crohn's disease (Pizarro, 2003). The complex, ashratide alone (reference), einautide alone (as a zinc(2+)-complex with histidine), and a combination treatment with both ashratide and einautide (again as a zinc(2+)-complex with histidine) were formulated and administered as an oral delayed release formulation according to Example 1 of EP 0 345 678 (comprising 60 percent by weight of the C_2-esterified alkoxylated polyol). To allow for oral administration to mice, 0.3 ml capsules were used containing the amount of active substance mentioned in the Table below.

The improvements of the disease scores were determined in the standard manner after 5 days of treatment and were expressed as a percentage over the improvement of the disease scores that was obtained with the reference (ashratide alone). The results are shown in Table B below:

TABLE B

Treatment	**Dose administered**	**Improvement *vs* reference**
Ashratide: (0.3 ml capsule with 2 mg ashratide/capsule)	16 mg/day (administered as 2 capsules 4x per day)	*[reference value]*
Einautide: (0.3 ml capsule with 2 mg einautide/capsule)	32 mg/day (administered as 4 capsules 4x per day)	+ 15 %
Ashratide: (0.3 ml capsule with 2 mg ashratide/capsule) *in combination with:* Einautide: (0.3 ml capsule with 2 mg einautide/capsule)	ashratide: 8 mg/day (administered as 1 capsule 4x per day); *and:* einautide: 16 mg/day (administered as 2 capsules 4x per day)	+ 10 %
Complex (0.3 ml capsule with 2 mg complex/capsule)	24 mg/day (administered as 3 capsules 4x per day)	+ 950 %

CLAIMS

1. The complex of ashratide, einautide and zinc(2+)-ions, in equimolar amounts.
2. Pharmaceutical composition comprising the complex of claim 1 and optionally one or more pharmaceutically acceptable carriers or excipients.
3. Pharmaceutical composition according to claim 2, which is in the form of a solution for injection or infusion.
4. Pharmaceutical composition according to claim 2, which is in the form of an oral delayed release formulation.
5. Complex according to claim 1, or pharmaceutical composition according to any of claims 2 to 4, for the treatment of inflammatory diseases.
6. Complex according to claim 1, or pharmaceutical composition according to claim 2 or 3, for the treatment of rheumatoid arthritis or lupus erythemathosus.
7. Complex according to claim 1, or pharmaceutical composition according to claim 2 or 4, for the treatment of Crohn’s disease or colitis ulcerosa.

Document D4: European application 1 234 567

Title: Spray for treating psoriasis

Applicant: Berlin Gesellschaft fur Technologische Forschung, GmbH,

Inventors: Baumann, P.; Schulze, K.

Priority date: December 15, 2006 (*)

Date of filing: December 14, 2007

Publication date: June 16, 2008

Designated Contracting States: BE, DE, FR, GB, IT, NL

(*) U dient er bij het beantwoorden van de opgave van uit te gaan dat de aanvrage zoals ingediend volledig gelijk is aan het prioriteitsdocument.

The present invention relates to a spray for treating psoriasis.

In our earlier European application 0 456 789, we described that the zinc(2+)-complex of ashratide and einautide provides a strong synergistic effect when used for the treatment of inflammatory disorders. We also showed that when this complex is formulated for oral delayed release administration, it can be used for the treatment of inflammatory disorders of the gastrointestinal tract, and that when this complex is formulated for infusion or injection, it can be used for the treatment of inflammatory disorders such as rheumatoid arthritis and lupus erythemathosus.

The very promising results described in EP 0 456 789 provide a strong rationale for attempts to try and apply the zinc(2+)-complex of ashratide and einautide for the treatment of psoriasis, another well-known inflammatory disease with a long-felt need for an effective treatment.

However, when trying to put this in practice, we encountered a number of technical challenges.

Firstly, as already mentioned in EP 0 456 789, in our research leading up to the invention described in our earlier patent, we found that administration of the zinc(2+)-complex of ashratide and einautide by injection or infusion (in amounts far exceeding the amounts that were effective in the treatment of rheumatoid arthritis) had no noticeable effect in an representative animal

model of Crohn's disease. Conversely, we found that oral delayed release administration of the zinc(2+)-complex in amounts that far exceeded the amounts that were found to be effective in an animal model for Crohn's disease, had not noticeable effect in a representative animal model of rheumatoid arthritis or lupus erythematosus.

As already mentioned in EP 0 456 789, and without being limited to any explanation or hypothesis, we believe that these findings are due to the known fact that einautide has a very limited ability to pass through epidermal layers. For example, it is already described in the Handbook of Pharmaceutical Sciences, 15th Ed. (2001), page 579, that for the treatment of psoriasis, the zinc(2+)/histidine-complex of einautide has to be applied topically to the skin, as administration by injection or infusion is not effective. Similarly, in our research leading up to the present invention, we tried whether administration of the zinc(2+)-complex of ashratide and einautide by injection or infusion (in amounts far exceeding the amounts that were effective in the treatment of reumatoid artritis) or oral delayed release administration of this zinc(2+)-complex (in amounts that far exceeded the amounts that were found to be effective in an animal model for Crohn's disease) could be used for the treatment of psoriasis in a standard animal model (Zenz en Wagner, 2005). Neither was found to be effective (data not shown).

In our further research leading up to the present invention, we did find that the zinc(2+)-complex of ashratide and einautide has therapeutic activity against psoriasis (and can indeed provide a synergistic effect compared to the use of ashratide alone, einautide alone, or ashratide and einautide in combination – see the data presented in Example 1 below), when this complex is applied directly to the skin. However, we also found that in order to obtain this therapeutic and synergistic effect, it is critical to keep a sufficient amount of the complex in contact with the skin, namely at least 9 mg/ml (see the results shown in Example 1 below).

This poses a further technical challenge, as the solubility of the complex in aqueous media is limited to about 9-10 mg/ml (again, due to the limited solubility of the einautide component of the complex).

As a result of our research, with the present invention, we now provide a solution for this problem, and so provide a way in which the synergistic effect of the zinc(2+)-complex of ashratide and einautide in respect of inflammatory diseases can also be put to use in the treatment of psoriasis.

Thus, according to the present invention, there is provided a spray that comprises an saturated solution (9-10 mg/ml) of the zinc(2+)-complex of ashratide and einautide in a pharmaceutically acceptable aqueous medium. It has been found that when this spray is applied to the affected areas of the skin at least once every 30 minutes (see Example 2 below), that the desired synergistic effect on the treatment of psoriasis is obtained.

As the aqueous medium for the spray, any suitable pharmaceutical buffer or aqueous medium can be used, as described in our earlier application EP 0 456 789. The saturated aqueous solution of the complex can also be prepared in the manner described in EP 0 456 789, for example by dissolving 650 mg einautide into a solution of 350 mg ashratide in 100 ml pharmaceutical phosphate buffer containing 0.1 M zinc-chloride. This solution can then be packaged in a suitable holder or container provided with means to dispense the solution and apply it to the skin as a spray or fine mist, such as bottle or ampoule with a hand-operated pump nebulizer or a pressurized container with a valve and spray nozzle.

As mentioned, in order to be active against psoriasis, this spray needs to contain at least 9 mg/ml of the complex (see Example 1), and must be applied to the affected areas of the skin at least once every 30 minutes (see Example 2).

Example 1: Determining the amount of complex required to provide a synergistic effect

Solutions containing different amounts of complex were applied to the skin of a mouse with psoriasis (Zenz and Wagner, 2005). To determine the amount of complex required, the solutions were applied to the skin as a fine mist every 5 minutes.

As a reference, a solution of an equimolar amount of ashratide (7 mg/ml) was used. It should be noted that, due to the known fact that einautide has a limited solubility in aqueous media (about 6-7 mg/ml, when formulated as a complex with zinc(2+) and histidine), it was not possible to prepare a solution that comprises an equimolar amount of einautide (which would have required a solution comprising 13 mg/ml einautide): instead, a saturated solution of the zinc(2+)/histidine-complex of einautide was used (i.e. with 6-7 mg/ml einautide). To determine the effect of ashratide and einautide in combination (but not as the complex of the invention), the application of the ashratide solution was alternated every 5 minutes with application of the einautide solution. All solutions were made using pharmaceutical phosphate buffer.

After 24 hours, the skin was evaluated for the psoriatic disease score. In the Table I below, these scores are expressed as percentage improvement compared to the reference (the 7 mg/ml solution of ashratide).

TABLE I

Solution applied	**Improvement in psoriatic score vs. the reference**
7 mg/ml ashratide	*[reference]*
Saturated solution of the zn(2+)/histidine complex of einautide (6-7 mg einautide/ml)	25 % worse than the reference
7 mg/ml ashratide, alternated every 5 minutes with a saturated solution of the zn(2+)/histidine complex of einautide (6-7 mg einautide/ml)	5 % worse than the reference
Complex, 7 mg/ml	5 %
Complex, 8 mg/ml	8 %
Complex, 9 mg/ml	95 %
Saturated solution of the complex (about 9-10 mg complex/ml)	175 %

Example 2: Determining the amount of complex required to provide a synergistic effect

To determine the frequency of application required, using the same animal model used in Example 1, a saturated solution of the complex (9-10 mg/ml) was applied to the skin at different intervals (every 5 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes and 1 hour, and after 24 hours the psoriatic scores were determined. The results were again expressed as a percentage improvement compared to the reference (a 7 mg/ml solution of ashratide applied at the same interval). The results are shown in Table II below.

TABLE II

Frequency of application	**Improvement in psoriatic score vs. the reference (applied at same interval)**
Every 5 minutes	175%
Every 10 minutes	180 %
Every 20 minutes	165 %
Every 30 minutes	170 %
Every 40 minutes	8 %
Every 50 minutes	5 %
Every 60 minutes	4 %

CLAIMS

1. Solution of the zinc(2+) complex of ashratide and einautide in a pharmaceutically acceptable aqueous medium wherein said solution comprises at least 9 mg of the complex per ml of the aqueous medium, for use in the treatment of psoriasis.

2. Solution according to claim 1, for application directly to (the affected areas of) the skin.

3. Solution according to claim 1 or 2, for application to (the affected areas of) the skin at least once every 30 minutes.

4. Solution according to any of claims 1 to 3, packaged in a suitable holder or container that is provided with means to dispense the solution and apply it to the skin as a spray or fine mist.

Document D5: European application 0 345 678

Title: Esterified alkoxylated polyols for use in pharmaceutical preparations.

Applicant: Redshift Chemical Company

Inventor: Fitkin, G.

Priority date: February 3, 2003

Date of filing: February 2, 2004

Publication date: August 5, 2004

Designated Contracting States: DE, FR, GB

The present invention relates to esterified alkoxylated polyols (“EAPs”) that can be used to prepare pharmaceutical formulations for topical administration of peptide-based drugs.

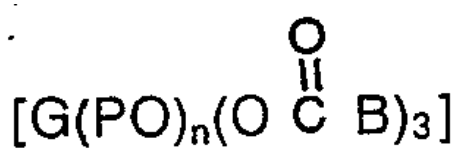
By "peptide-based drug" is generally meant any peptide drug with a molecular weight of less than 75kD (or any suitable combination of such peptides).

As used herein, "topical administration" of such a peptide-based drug generally involves bringing the peptide drug into contact with an epidermal layer of the subject to be treated, such as the skin or the wall of the gastrointestinal tract.

It is generally known that polyols and polyol derivatives can be used for preparing pharmaceutical formulations for topical administration of peptide-based drugs. However, compared to the use of known polyols and polyol derivatives that can be used for the preparation of topical formulations of peptide drugs, the esterified alkoxylated polyols of the present invention have the advantage that they have strong(er) film-forming properties. This for example allows for a protective layer to be formed on the epidermal layer to which the formulations of the invention are applied, which in turn allows the peptide-based drug to remain in contact with the epidermal layer for an extended period of time.

Thus, generally, the invention relates to the esterified alkoxylated polyols (“EAPs”) described herein, as well as to pharmaceutical compositions (in particular, for topical use) that comprise at least one therapeutically active peptide-based drug and at least one such EAP.

The esterified alkoxylated polyols ("EAPs") of the invention have the general formula:



in which:

- "PO" represents a C_3-C_6 oxyalkylene unit derived from an epoxide, such as oxypropylene (preferred), trimethylene oxide, 1,2-butene-oxide or allyl-glycidyl-ether.
- "G" is an organic radical derived from a polyol, i.e. a polyhydric alcohol with between 2 and 8 hydroxyl groups. Examples are diols, (such as ethylene glycol), triols (such as glycerol), saccharides (such as glucose and fructose) and sugar alcohols. Glycerol is preferred.
- Each "B(C=O)O-" ester group is derived from a long chain C_8-C_{24} fatty acid (so that each "B" is a C_7-C_{24} hydrocarbon group). Examples of suitable ester groups are ester groups derived from caprylic acid, lauric acid, stearic acid, palmitic acid (preferred), linoleic acid, linolenic acid, oleic acid (preferred) and heptadecanoic acid (also preferred) and other naturally occurring saturated or unsaturated fatty acids such as fatty acids derived from coconut oil, palm oil, peanut oil and sunflower seed oil; and
- "n" is an average number between 2 and 18, preferably between 8 and 12.

The EAPs of the invention can be prepared in a manner known per se, for which reference is made to the standard handbooks, such as the Handbook of Organic Polymer Chemistry, 10th Edition, 1998. Usually, the polyol is first alkoxylated with the epoxide, and then esterified with the fatty acid (see Example 1 below).

The esterified alkoxylated polyols described herein can generally be used for the formulation of any peptide-based drug, as long as the peptide-based drug is compatible (e.g., in terms of solubility, storage stability, etc.) for formulation with polyols and polyol derivatives. The skilled person can easily determine this experimentally by contacting the desired amount of the peptide drug with the esterified alkoxylated polyols (in the amount prescribed herein) in the intended pharmaceutical buffer. Alternatively, some handbooks (such as the Handbook of Pharmaceutical Sciences) give information on the compatibility of peptide drugs with polyols.

Preparations based on the EAP's of the invention contain between 0.1 and 10 mg of the peptide drug per unit dose (i.e. per ml of the formulation or per capsule).

The present invention envisages that the formulations described herein can be used for administration of the peptide-based drugs to either the wall of the intestine or to the skin.

For example, oral delayed release capsules for administration to the walls of the intestine may for example have the following composition:

Oral delayed release capsules

Component	**Amount (percent by weight of total composition)**
EAP of invention	70-80 %
Solution of peptide-based drug (5-15 mg/ml) in a suitable aqueous carrier such as a pharmaceutical buffer	20-30 %
Further suitable excipients known per se	Suitable amounts known per se, not exceeding 5% by weight.

To prepare the capsules, the EAP may be added to the solution of peptide, at a temperature between 60-70°C and under vigorous stirring. The viscous mass may then be fed to a capsule-forming machine operating at a temperature of about 50°C. After cooling to below 40°C, semi-solid capsules containing between 2.5 and 7.5 mg of the peptide per capsule are obtained, which may optionally be coated, for example with a hard-shell sugar coating or with an enteric coating known per se.

With advantage, and as is known for semi-solid capsules based on polyol derivatives, the capsules of the invention are resistant to stomach acids and allow for delayed release of the peptide-based drug in the intestines. Thus, it is envisaged that the capsules of the invention (that slowly fall apart in the intestines, forming a viscous coating layer on the intestinal wall) can be used with advantage for oral administration of peptide-based drugs that are intended for the treatment of intestinal disorders, such as Crohn's disease or colitis ulcerosa.

A cream for topical application to the skin may for example have the following composition:

Cream for topical administration to the skin

Component	**Amount (percent by weight of total composition)**
EAP of invention	50-60 %
Solution of peptide-based drug (5-10 mg/ml) in a suitable aqueous carrier such as a pharmaceutical buffer	40-50 %
Further suitable excipients known per se	Suitable amounts known per se, not exceeding 5% by weight.

To prepare the cream, the EAP may be added to the solution of the peptide, at a temperature between 60-70°C and under vigorous stirring. After cooling to ambient temperature, a cream is obtained that contains between 2.5 and 5 mg of the peptide per ml of the cream.

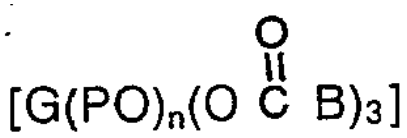
The cream thus obtained can then be applied to the skin, whereupon it forms a layer that not only protects and hydrates the skin, but also allows the active substance contained in the cream to stay in contact longer with the skin to be treated (see Example 3 below).

Depending on the peptide-based drug that is included in the cream, this preparation may be used for treatment of various skin diseases such as acne, eczema, yeast infections such as athlete's foot or *Candida* infections, or inflammatory skin diseases such as dermatitis or psoriasis. It is also envisaged that the EAP's of the invention can be used in other preparations that are intended for application to the skin, such as suncreams, handcreams and cosmetics.

Example 1: preparation of esterified alkoxylated polyols ("EAP")

Glycerol was alkoxylated with propylene oxide (about 10 mol per mol glycerol used), using potassium hydroxide as the catalyst. These base-catalysed conditions led to an intermediate alkoxylated polyol with more than 95 % secondary hydroxyl end-groups and less than 5% primary hydroxyl-end groups.

The available hydroxyl groups in this intermediate were then esterified with an excess amount of palmitic acid, to form the esterified alkoxylated polyol of the formula



in which n is an average number of about 10, "PO" is the oxypropylene unit derived from the propylene oxide, "G" is a glyceryl radical derived from the glycerol, and the ester moiety "B(C=O)O-" is derived from the palmitic acid. The EAP was then isolated and purified in a manner known per se.

The alkoxylation and esterification reactions can be performed using solvents and further conditions known per se, for which reference is for example made to the Handbook of Organic Polymer Chemistry, 10th Edition, 1998.

Example 2: improved film-forming properties of an EAP-based cream

A cream was prepared with the following composition: 55% by weight of the EAP of Example 1, 45 % distilled water, and 0.5 mg/ml carmine red, a colorant used as the red color in cosmetics.

To determine the film-forming properties of the cream, the cream was applied (in squares of 3 x 3 cm) to the skin of New Zealand White rabbits (which are also used in standard tests for primary skin irritation), which were then allowed to run freely in their cages (for the time indicated in the next paragraph). For comparison, a number of creams each containing 45% by weight of a known commercially available polyol derivative for skin creams comprising 0.5 mg/ml carmine red were used.

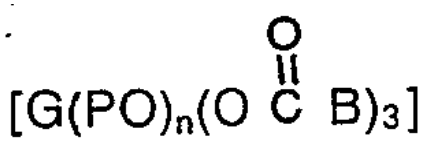
After that, the amount of cream still present on the skin of the rabbits (as measured by both the remaining size of the applied square, the intensity of the remaining red color and the overall appearance of the applied squares) was determined after 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, 2 hours, and thereafter every hour for the next 12 hours.

With the creams of the invention, the squares with the red colorant remained on the skin of the rabbits up to 12 hours. With the creams based on conventional polyol derivatives, the red squares had essentially disappeared after only 2-3 hours.

Thereafter, the rabbits were also scored for skin irritation (i.e. for erythema (redness) and edema (swelling)) after 24, 48 and 72 hours, in accordance with known toxicological standards for skin preparations. No visible skin irritation was observed.

C L A I M S

1. Esterified alkoxylated polyol of the formula:



in which:

- "PO" represents a C_3-C_6 oxyalkylene unit derived from an epoxide;
- "G" is an organic radical derived from a polyhydric alcohol with between 2 and 8 hydroxyl groups;
- Each "B(C=O)O-" ester group is derived from a long chain C_8-C_{24} fatty acid; and
- "n" is an average number between 2 and 18.

2. Esterified alkoxylated polyol according to claim 1, in which:

- "PO" represents a C_3 oxyalkylene unit derived from oxypropylene;
- "G" is an organic radical derived glycerol;
- Each "B(C=O)O-" ester group is an ester group derived from palmitic acid, oleic acid or heptadecanoic acid; and
- "n" is an average number between 8 and 12.

3. Pharmaceutical composition comprising at least one therapeutically active peptide-based drug and at least one esterified alkoxylated polyol according to claim 1 or 2.

4. Pharmaceutical composition according to claim 3, which is in the form of an oral delayed release formulation, which for example comprises a peptide-based drug for the treatment of Crohn's disease or colitis ulcerosa.

5. Pharmaceutical composition according to claim 3, which is in the form of a cream for application to the skin, which for example comprises a peptide-based drug for the treatment of acne, eczema, yeast infections such as athlete's foot or *Candida* infections, or inflammatory skin diseases such as dermatitis or psoriasis.