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Title: PROPHYLACTIC AND THERAPEUTIC TREATMENT OF MIGRAINE AND MIGRAINE-RELATED DISEASES WITH MACROLIDE AND/OR TETRACYCLINE COMPOUNDS AND/OR GYRASE INHIBITORS

Abstract: The invention relates to the use of compounds, which belong to the families of macrolides, tetracyclines and gyrase inhibitors, for the manufacture of a pharmaceutical composition for the prophylaxis and avoidance and for the therapeutic treatment of acute and chronic headaches, which are associated with migraine or migraine-related diseases.
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Prophylactic and therapeutic treatment of migraine and migraine-related diseases with macrolide and/or tetracycline compounds and/or gyrase inhibitors

Field of the invention
The present invention relates to the use of at least one macrolide compound and/or at least one tetracycline compound and/or at least one gyrase inhibitor for the manufacture of a pharmaceutical composition for the prophylaxis and prevention as well as for the therapeutic treatment of acute or chronic headaches, which are associated with migraine or migraine-related diseases.

Several documents are cited throughout the text of this specification. Each of the documents cited herein (including any manufacturer’s specifications, instructions, etc.) are hereby incorporated in its entirety by reference. However, there is no admission, whatsoever, that any of the cited documents is indeed prior art as to the present invention.

Background of the invention
Migraine and migraine-related diseases, which are associated cerebral headache, are very common diseases in humans of both sexes. About 16 % of the world population are affected (STEWART, W.F. et al., Neurology 44 (suppl. 2): 17-23). The prophylactic and the therapeutic treatment of this acute and chronic disease has major economic relevance, because such condition of pain already occur at a relative young age, which impair strongly the quality of life of affected persons with increasing age. Moreover, the condition of pain as a consequence of a migraine attack and further concomitant phenomena (for example vomiting, nausea, photophobia, phonophobia) are so intense that a quick, effective and lingering relief is necessary, especially because secondary mental alterations are common.
Migraine is today understood as a chronic or acute paroxysmal disease with attacking headaches and with mostly one-sided, pulsatile or pulsatile symptoms of pain. Light and noise sensitivity, nausea and vomiting are typical secondary manifestations of this disease. Further, it is known that neurological deficits precede the actual migraine attack. In this case, it is referred to migraine with aura. According to today's standard of knowledge, the typical migraine, with or without aura, is not based on a psychosomatic genesis, but rather on a biological, cerebral disorder. Typically, the actual migraine attack is preceded by a prodromal stage, which, for example, is expressed by fatigue, appetite, disorder of motivation and edema. Because of these defined precursors, it is possible that the affected migraine patient can very easily take prophylactic measures before the actual migraine attack begins. The so-called cluster headache (Bing Horton's Syndrome) occurs mostly without prodromal stage.

Even though the pathogenesis of migraine is not fully elucidated yet, apparently changes of the vascular zone of cerebral vessels, an excessive prostaglandin distribution and defects of the serotonin regulation or the status of the receptor and a degranulation of mastocytes are involved. This may additionally result in an aseptic inflammatory reaction in perivascular parts of dura arteries, whereupon the typical headache develops. Further participation of vegetative centers in the brain stem then cause nausea, vomiting, sweating, hypotonia and uriestesia (DIENER, H.-C. and MAY, A., Internist 35: 26-31, 1994). Furthermore, the interference with ion channels can modulate the severity of pain attacks.

Migraine and its related forms are today taxonomically summarized under the category vascular headache, according to "World Federation of Neurology" and "International Headache Society (IHS)". Accordingly, vascular headaches comprise per definition migraine as such (with or without aura, depending on typical prodromal symptoms), cluster headache including their episomic and chronic forms, toxic vascular headache and hypertensive headaches. Furthermore, among migraine-related diseases are hemiplegic migraine, ophthalmological migraine, basilar arterial migraine and menstrual migraine. The classification committee of IHS defines migraine in general as an "idiopathic, recurrent headache disease, which is expressed in pain attacks between 4 to 72 hours" and which is typically unilaterally localized and accompanied by nausea, photophobia, phonophobia and strong pulsatile pain conditions, which are aggravated by physical activities (DIAMOND,
S., Compr. Ther. 21(9): 492-498, 1995). Due to these accurate criteria for diagnosis and classification, it is possible to clearly distinguish the type of headache of migraine and migraine-related diseases from all other kinds and reasons of headaches.


However, until now the mechanisms and reasons, which lead to migraine and its further forms and sub-forms, are widely unexplained.

According to more recent studies, the stimulation of serotonin receptors (5-hydroxytryptamin receptors, 5-HT receptors) is alternatively discussed as pathophysiological reason of migraine and migraine-related attacks (PEROUTKA, S., Neurol. Clin. 8: 829-839, 1990; PEROUTKA, S., Ann, Rev. Neurosci. 11: 45-60, 1988), among which five different sub-types (5-HT_{1A}, 5-HT_{1D}, 5-HT_{1C}, 5-HT_{2} and 5-HT_{3}) are known to date.

According to this, as the underlying rationale for a therapeutic or rather symptomatic (abortive) and prophylactic treatment of migraine, an interaction of known anti-migraine agents with specific 5-HT receptor subunits is used, especially because most known medicaments of this type are known as serotonin agonists or serotonin antagonists. Therefore, the state of the art prophylaxes and therapy of migraine and migraine-related diseases comprises in particular such active compounds as for instance amitriptyline, cyproheptadine, pizotyline, methysergide, pizotifen, secale alkaloids (in particular ergotamine or dihydro-ergotamin [DHE]), sumatriptan, propanolol or trimolol, which in particular show affinity for 5-HT_{1D} or 5-HT_{1A} receptors. They act by inhibiting the tachykinin release from trigeminal nerve fibers via respective receptors, which is in particular true for DHE and sumatriptan. Additionally, also 5-HT_{2} antagonists are administered for prophylaxis, like for instance cyproheptadine, methysergide, pizotifen, amitriptyline or verapamil (SOLOMON, G.D., J. Clin. Pharmacol.
32: 200-209, 1993), because 5-HT2 antagonists are only of minor therapeutical value (PEROUTKA, S., 1990, loc. cit.).

In addition to the above-mentioned active compounds also non-steroidal anti-inflammatory drugs (NSAIDs), for instance flurbiprofen, are suggested for prophylactic treatment, which prophylactic effect shall either be mediated by 5-HT receptors or by inhibition of vascular inflammations (SOLOMON, G.D., J. Clin. Pharmacol. 33: 200-209, 1993).

On basis of the above-mentioned prior art, it is today assumed that active compounds, which inhibit the release of tachykinin inhibitors (as for instance sumatriptan or ergotamin) or which inhibit neurological inflammatory processes (as for instance non-steroidal, anti-inflammatory active compounds, NSAIDs), have to be used for the therapeutic and symptomatic (abortive) treatment of migraine or migraine-related diseases. In contrast to this, active compounds, which block the trigeminovascular stimulation (as for instance beta blockers, calcium antagonists, antidepressants, NSAIDs, methysergid) shall be considered for the prevention and prophylactic treatment of migraine or migraine-related diseases.

More recently, the 5-HT1D receptor agonist sumatriptan, which exerts a vasoconstrictory effect (possibly by the inhibition of the release of tachykinin) and which increases the blood circulation rate in cerebral artery, has been favored for migraine treatment and symptomatic medication (DIENER, H.C., Internist 24, 63-66, 1993). The bioavailability of sumatriptan is subcutaneously 96 %, however after oral application it is only 14 %, and its half-life is 2 hours on the average (DIENER, H.C. 1993, loc. cit.; SOLOMON, G. D., J. clin. Pharmacol. 33: 200-209, 1993). It has turned out as a disadvantage that sumatriptan induces breast symptoms with indications of cardial ischemia, that headaches reoccur after an initial successful treatment and that a sumatriptan addiction exists together with the appearance of "sumatriptan-related headaches" (FERRARI, M.D.and HAAN, J., Curr. Opin. Neurol. 8, 237-242, 1995).

Furthermore, the GABA (gamma amino butyric acid) agonist valproate was used in order to effectuate a migraine prophylaxis by dilatation of cerebral arteria (HERRING, R.and KURITZKY, A., Cephalalgia 12: 81-84, 1992; MATTEW, N. and ALI, S., Headache 31: 71-74, 1991).
In particular beta blocker (as for instance propanolol, timolol, nadolol, metaprolol or atenolol), calcium channel blocker and calcium antagonists (as for instance verapamil, nifedipin) and NSAIDs are suggested as agent of choice for prophylactic treatment (SOLOMON, G.D., J. Clin. Pharmacol. 33: 200-209, 1993). However, beta blocker have the disadvantage that they are contraindicated in patients with congenital heart defects and with a plurality of further diseases (asthma, emphysema, chronic bronchitis, diabetes Wolff-Parkinson-White syndrome). Additionally, they lead to exacerbation of the Raynauds syndrome, which occurs in migraine patients, and also lead to depression, fatigue and insomnia. Even though verapamil and flunarizin have prophylactic potential, calcium antagonists, however, show the disadvantage that they induce heart damages or, in case of nifedipin, may cause dramatic vasodilatations. Additionally, further serious side effects, as for instance sedation, weight gain, parkinsonism, edemata and gastrointestinal disorders are known (for example nimodipin, verapamil).


Drawbacks are also the various and severe side effects of NSAIDs, among which are known for instance digestive disorders, heartburn, nausea, vomiting, diarrhea, constipation, abdominal pain, bleeding in the upper gastrointestinal region and kidney disorders caused by reduced glomerula filtration.


Further, it is an additional general disadvantage of the presently known anti-migraine agents, that these agents do not display the desired effect in all cases; that they do not show a simultaneous prophylactic and therapeutic potential, so that different active compounds have to be used; that most of them only reduce the frequency of migraine attacks and that they
cannot entirely and permanently eliminate migraine or migraine-related diseases and pain conditions related thereto; that they are contraindicated in many cases and may not be taken for a longer period. Additionally, in particular with cluster headache, most symptomatically acting active compounds are ineffective (DIENER, H.C., Eur. Neurol. 34 (suppl. 2): 18-25, 1994; DIAMOND, S. 1995, loc. cit.).

Last but not least due to manifold and severe side effects and the complexity of today's available anti-migraine agents for prophylaxis and therapy, which effects are additionally often unsatisfying, experts today believe that there is a great need for an improved migraine therapy. However, new active compounds will not be used in clinical application over the next years (FERRARI, M.D. & HAAN, J., Curr. Opin. Neurol. 8: 237-242, 1995).

Accordingly, no safe and effective medicament for the prophylactic and therapeutic treatment of migraine and migraine-related diseases are available in the prior art.

Summary of the invention
It was an object of the present invention to provide an active compound and/or a group of active compounds for the prophylactic and therapeutic treatment of migraine and migraine-related diseases, to overcome the disadvantages of the prior art.

It has been surprisingly found by the inventor of the present invention that macrolide compounds, tetracycline compounds and/or gyrase inhibitors are highly effective in the prophylactic and therapeutic treatment of migraine and migraine-related diseases.

Therefore, the present invention provides for compounds of the groups of macrolides, tetracyclines and/or gyrase inhibitors which are used for the manufacture of a pharmaceutical composition for the prophylaxis and prevention and for therapeutic treatment of acute and chronic headaches, which are associated with migraine or migraine-related diseases.

Detailed description of the invention
In a first embodiment, the present invention relates to the use of at least one macrolide compound and/or at least one tetracycline compound and/or at least one gyrase inhibitor,
analogues, derivates and/or stereoisomers thereof, pharmaceutically and physiologically harmless acid addition salts and mixtures thereof for the manufacture of a pharmaceutical composition for the prophylactic and/or therapeutic treatment of migraine and/or migraine-related diseases.

Examples for macrolides, tetracyclines and gyrase inhibitors are described in detail in the following. According to the invention, all derivatives of these compounds can be used. They can be derived from macrolide, tetracycline and quinolone carboxylic acid basic structure. Further, analogues of these compounds can be used, which are compounds comprising a comparable basic structure and therefore exert comparable effects. An example for such analogues are aza analogues of quinolone carboxylic acids. Furthermore, stereoisomers and pharmaceutically and physiologically harmless acid addition salts of these compounds can also be used. In this invention, it is always a prerequisite that they comprise comparable effects as macrolide and tetracycline compounds and gyrase inhibitors and their aza analogues. The active compounds are used together with pharmaceutically harmless, carriers, auxiliary substances and excipients, diluents etc. in form of appropriate preparations.

Compounds comprising macrolide, tetracycline and gyrase inhibitor effects, are known in the prior art. Also their preparation, pharmacology, metabolism and their clinical investigations have been described for their sole use as antibiotic agents. For disclosure it is for example referred to Ernst Mutschler, Arzneimittelwirkungen, Lehrbuch der Pharmakologie und Toxikologie, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 2001.

It was surprising and totally unexpected by a skilled person that migraine and migraine-related diseases can be efficiently treated prophylactically and therapeutically with the above-mentioned compounds. It was particularly surprising and it is considered to be a major advantage that a quick and sustained elimination of migraine-typical symptoms, in particular of headaches, can be achieved in vivo in humans. Further, it was surprising that also strongest, so far absolutely therapy resistant pain symptoms, as they are for instance typical with episodic and chronic cluster headache, were quickly eliminated with the composition according to the present invention comprising the above-mentioned compounds. Moreover, there was no recurrence of headaches under permanent medication.
This was rather surprising, as macrolides, tetracyclines and gyrase inhibitors, which were used in the prior art as antibiotic agents led to an adaptation to the active compound.

The active substances of the present invention, which were applied before the occurrence of a migraine attack, which was announced by the typical prodromal stages, a symptom-free interval over several weeks and months for the entire duration of the application was achieved.

Even with higher individual medication and with permanent medication none of the objectively and subjectively asserted side effects occurred, which are known from previous migraine treatments. This is additionally advantageously, in particular for patients who suffer from chronic migraine and chronic cluster headache with strong and strongest pain symptoms.

The terms “treatments”, “treating” and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of partially or completely curing a disease and/or adverse effect attributed to the disease. The term “treatment” as used herein covers any treatment of a disease in a mammal, particularly a human and includes (i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e. arresting its development; or (iii) relieving the disease, i.e. causing regression of the disease.

The term "pharmaceutically acceptable" means a non-toxic material, which does not negatively influence the effect of medically active substance.

In a further embodiment of the invention, the pharmaceutical composition for the prophylactic and/or therapeutic treatment of migraine and/or migraine-related diseases comprises a pharmaceutically and physiologically acceptable carrier, auxiliary substance and/or excipient.
If the active compound is a macrolide compound, it is particularly advantageous selected from the group consisting of azithromycin, dirithromycin, spiramycin, josamycin, erythromycins and clarithromycins and mixtures thereof.

It is an additional advantage of the compounds according to the present invention that most of them are well investigated and known with respect to toxicology, pharmacology, metabolism, side effects, compatibility and dosages, so that these data and parameters can be easily conferred to the use according to the present invention.

For example, for the macrolide Klacid® (clarithromycin) it is known that this compound, even after high oral dosage of up to 1,000 mg as single dose does not show any measurable side effects or abnormalities with respect to physiological parameters or clinical data and is assessed as a secure and non-toxic active compound.

Furthermore, it is an advantage that the compounds according to the invention do not lead to addiction and therefore, can be used for a long-term treatment.

In a further embodiment of the present invention, the tetracycline compound is selected from the group consisting of tetracycline, oxytetracycline, doxycycline, minocycline, demeclocycline, metacycline and rolitetracycline and mixtures thereof.

In yet another embodiment of the present invention, the gyrase inhibitor is selected from the group consisting of quinolone carboxylic acid, cinoxacin, pipemidic acid, norfloxacin, ciprofloxacin, ofloxacin and enoxacin and mixtures thereof.

It is particularly preferred if the quinolone carboxylic acid is nalidixic acid.

It is preferred to use a combination of different active compounds, and in particular, the pharmaceutical composition may comprise at least one macrolide compound and at least one tetracycline compound. Both active substances may be included in one single form suitable for administration to a patient. Alternatively, it is also contemplated that both active compounds are administered in separate form. The macrolide compound and the tetracycline compound can be applied sequentially or simultaneously.
Also a combination of at least one gyrase inhibitor and at least one macrolide compound and/or at least one tetracycline compound can be used. It is preferred to combine all active compounds to be used in one single form suitable for administration to a patient. However, it is also possible to administer the gyrase inhibitor and the macrolide compound and/or the tetracycline compound are applied sequentially or simultaneously in two or three independent pharmaceutically and physiologically acceptable forms.

In an alternative embodiment, the pharmaceutical composition comprises at least two macrolide compounds and/or tetracycline compounds and/or gyrase inhibitors. The use of more than one active compound has the advantage that the individual dosage of each compound can be reduced. Further, it has been demonstrated that the combination of different active compounds leads to a synergistic effect, which exceeds the addition of the individual effects.

The manufacture of macrolides, tetracyclines and gyrase inhibitors is described in the prior art, and according to the description in literature they can e.g. be administered by the oral route and/or parenterally. Other kinds of application, such as transdermal systems or inhalation are also enclosed.

The properties of the auxiliary substances and excipients will depend from the form of application. Techniques for formulation and application of the compounds used according to the present invention can be found for instance in Remington’s Pharmaceutical Sciences, Mac Publishing Corporation, Easton, PA, latest edition.

The manner of application complies with the needs of the patient, the kind and the severity of the disease and whether a prophylaxis or therapy of the disease is intended. Further, it has to be considered whether the active compounds are used individually or in combination with each other. If the compounds are administered in combination with each other, the invention comprises a serial or a simultaneous application.
After oral application, older tetracyclines are incompletely resorbed in the intestine, while the more lipophilic substances doxycycline and minocycline are almost completely resorbed. Rolitetracycline is in particular applied parenterally.

The therapeutic effective amount of the compound or the compounds to be applied, is determined in clinical trials and on the individual patient.

For instance, tetracyclines can be isolated from different streptomycye species. However, many of the known compounds can be manufactured partly synthetically or entirely synthetically. The compounds of the tetracycline group have a common basic structure of four anneled six-rings, and they are distinguished from each other with respect to their chemical structure only in different ring substituents. Examples for such compounds are tetracycline, oxtetracycline, demeclocycline, doxycycline, minocycline and rolitetracycline.

So far, tetracyclines have been described as broad-spectrum antibiotics. The inhibition of the ribosomal protein synthesis has been described as the mode of action. The low toxicity is based on a much higher affinity of tetracyclines to bacterial ribosomes in comparison to mammal ribosomes. With the exception of their bacteriostatic effect no other effects, in particular the effects as claimed herein, are known.

In the following, some tetracycline compounds and most often used product trademarks are cited. The product trademarks are protected trademarks.

**Tetracyclines:**

- Tetracycline preparations:
  - Achromycin 500
  - Achromycin ointment
  - Imex
  - Mysteclin
- Polcortolon TC spray
- Supramycin pro infusione
- Tefilin
Tetracyclin-Hayl 500
Tetracyclin-ratiopharm
Tetracyclin Wolff
Tetralution 500

5 Oxytetracycline
  preparations:
  Corti Biciron N
  FARCO-TRIL
  Oxy Biciron

10 Oxytetracyclin 250 mg JENAPHARM
    Oxytetracyclin ointment 1% SR
    Terracortril creme; ointment; spray
    Terramycin eye ointment
    Terramycin ointment

15 Terramycin vaginal tablets
    Tetra-Gelomyrtol

Doxycycline
  preparations:
  Ambrodoxy

20 Ambroxol AL comp.
    Ambroxol comp.-ratiopharm
    AMDOX-PUREN
    Azudoxat/-200 mg tablets; -100 tabs/-200 tabs
    Azudoxat comp.

25 Clinofug D 50
    DOXAKNE tabs
    Doxam
    Doximucol
    Doxy 100/-200 – 1 A Pharma

30 Doxy 100/-200 from ct; -100/-200 from ct tablets
    Doxy 100 mg/-200 mg AbZ tablets
    Doxy 200/-Komb.
    Doxy-acis 100 mg
Doxy comp. from ct
Doxycyclin 100/-200 Heumann
Doxycyclin 100 mg JENAPHARM
Doxycyclin AL 100/-200; -100 T/-200 T
Doxycyclin Atid 100 mg
DOXYCYCLIN BASICS 100 mg/-200 mg
Doxycyclin-Heyl 100/-200
Doxycyclin PB 100 mg/-200 mg
Doxycyclin-ratiopharm 100; -SF
Doxycyclin STADA 100/-200 tabs; -100 mg/-200 mg film tablets
Doxyderma 50/-100
Doxy-Diolan 100 mg/-200 mg
Doxydoc 100
Doxy-duramucal
Doxynexal/-200; -tabs/-200 tabs; -SF
Doxy-HP 100 mg/-200 mg
Dox Lodoxyl
Doxi M 100/-200 from ct
Doxymerck 100 mg/-200 mg
Doxymono 100/-200
Doxym M-ratiopharm 100/-200 tablets
Doxy.N. tablins/-forte-tablins
Doxy plus STADA
DOXY-PUREN
Dox S+K
Doxysolvat
Doxy-Wolff 100/-200; -100/-200 Tabs
Doxy-Wolff Mucolyt.
Jenabroxol comp.
Jenacyclin 100 mg/-200 mg
Mespafin 100
Neodox /-forte
Sigadoxin /-200; -Tabs
Sigamuc
Supracyclin Tabs 100/-200
Terelit
Vibramycin N; -Tabs
Vibravenös SF

Minocycline preparations:
AKNE-PUREN
Aknin-Mino

Aknosan
Klinomycin 50
Klinomycin 100
Lederderm 50/Lederderm-long
MINAKNE

Minocyclin 50 mg
Minocyclin 50/-100 Heumann
Minocyclin 50 from ct
Minocyclin beta 50
Minocyclin-ratiopharm 50/-100

Minocyclin STADA 50 mg
Minoplus /-forte
Mino-Wolff 50 mg
Skid /-100 mg
Skinocyclin

Udima 50/-100

Demeclocycline
Methacycline

Macrolides are antibiotics, which are recovered from streptomyces species and comprise a macrocyclic lactone ring and sugars bound by a glycoside bond. Their bacteriostatic effect on different germs is known. Among the macrolides of the erythromycin group are for example erythromycin, spiramycin and josamycin.
It has been found as a mode of action that macrolide antibiotics inhibit the protein synthesis in the elongation phase by influencing the translocation.

Erythromycin is inactivated in the acid environment of the stomach. In order to improve the resorption at oral application, the substances are partly applied in esterified form.

In the following, some examples for macrolide compounds and their trade names are given. The trade names are protected trademarks.

10 **Macrolides:**

Azithromycin
  preparations:
    Ultreon
15  Zithromax 250 mg film tablets; -powdered juice
    Zithromax Uno
Clarithromycin
  preparations:
    Biaxin HP
20  Cyllind
    Klacid /-PRO/-forte 500 mg; -drink 250 mg; -juice/-forte; 250 mg/5ml
    Mavid
    ZacPac
Dirithromycin (active metabolite erythromycin)
25  Erythromycin
  preparations:
    Akne Cordes solution
    Aknederm Ery Gel 2%/-4%
    Aknefug-EL
30  Aknemycin
    Aknemycin-2000
    Aknemycin Plus
    Clinesfar Gel
Ecolicin
Ery 500–1 A Pharma
Eryaknen 2%/-4%
Erybeta 500: -TS/-TS forte
ERYSICNUM i.v. 0.5 g/i.v. 1 g CytoChemia
ERYDER MEC 2%/-4% Gel
Ery-Diolan 200 mg ; -500 mg
Ery-hameln 1000 mg
Eryhexal 500; -500/-1000; -juice/-forte juice
ERYTHRO 500 from ct : -1000 from ct granulate ; erythro from ct
ERYTHROCIN 500 Neo; -1000; -0.5 g/-1.0 g
ERYTHROGENAT; -TS
ERYTHRO-HEFA 500
ERYTHROMYCIN 500 Heumann
ERYTHROMYCIN 500 mg curasan
ERYTHROMYCIN acis 500 mg; 4% juice
ERYTHROMYCIN AL 500
ERYTHROMYCIN-ratiopharm 250 DB/-500 DB/-1000 DB; -500
ERYTHROMYCIN-ratiopharm TS/-forte ratiopharm TS
ERYTHROMYCIN STADA 500 mg; -1000 granulate/-powdered juice
ERYTHROMYCIN-WOLFF; film tablets
Hydrodermed Ery 2%/-4%
Inderm
Inderm Gel 2%/-4%
INFEKTOMYCIN 100/-200/-400/-600 juice
INFEKTOMYCIN basic juice 200
ISOTREXIN Gel
KAREX-WOLFF 650
MONOMYCIN; -juice/-baby juice
PAEDIATROCHIN/-forte; child drops
SANASEPTON Gel 2%/-4%
SANASEPTON powdered juice 200 mg/5 ml/-Forte 400 mg/5 ml
Stiemycine
Synergomycin baby drops; -powdered juice
Zineryt

Spiramycine

preparations:
Rovamycine-1 500 000 I.E.
Selectomycin

Gyrase inhibitors are derivates of quinolone carboxylic acid and their analogues, preferably aza analogues, which are antibacterially effective and act as inhibitor of subunit A of DNA gyrase. Their bactericide effect is known. Among the gyrase inhibitors of the first generation are substances like nalidixic acid (commercial product, e.g. Nogram), cinloxacine (commercial product, e.g. Cinobactin), pipemidic acid (trademark, e.g. Deblaston). Among the gyrase inhibitors of the second generation are for example norfloxacine (commercial product, e.g. Barazan), ciprofloxacin (commercial product, e.g. Ciprobay), ofloxacine (trademark, e.g. Tarivid) and enoxacin (trademark, e.g. Gyramid).

It is emphasized that the above cited single compounds of compound families of macrolides, tetracyclines and gyrase inhibitors are exemplarily given only. Due to their common structure elements it is contemplated that all components of the cited compound families have the herein claimed effects. Therefore, the invention also comprises such compounds, which have been developed from the cited compounds as starting material or will be developed, provided that they comprise structural similarities and/or the effects of macrolides, tetracyclines and/or gyrase inhibitors according to the present invention.

From the prior art it is already known that the above cited compounds comprise different bacteriostatic and bactericide effects. The compounds may be differentially active against different bacterial strains, i.e. they may comprise a different spectrum of action. Similarly, the above cited compounds may also certainly be differentially active in the present form of administration, depending on the patient and on the type and severity of the disease. This is a common phenomenon in medical science. However, due to their common structure, all cited compounds show the claimed effect. On the basis of the present description, the person skilled in the art may test in routine experiments, which of the compounds is particularly ef-
ffective and particularly acceptable in the individual patient. For this, no inventive step is necessary.

For applying the compounds on which the present invention is based, they are mixed with known, common auxiliary substances and excipients, according to the respective galenic application form, and formulated.

The respective therapeutically active dose depends on the type (for instance acute or chronic) and the severity of the migraine form to be treated and on the individual response to a primary dosage. For example with chronic migraine or chronic cluster headache, preferably a long-term treatment may be considered, which is likewise possible with a prophylactic treatment. In acute migraine attacks, rather a short-term treatment will be intended.

According to this, the compounds of the present invention have to be chosen according to the bioavailabilities and half-lives.

Because the dosages of the compounds according to the present invention are generally known and described in literature, and because these dosages show extraordinarily good effects also in the uses according to the present invention, these known dosage recommendations can be simply accepted for the purpose of the present invention.

However, not only the individual substance may advantageously be administered, but also a combination of the compounds according to the present invention with either macrolide, tetracycline or gyrase inhibitor effects, if that measure is necessary for medical grounds.

According to this, the present invention also comprises combinatorial preparations, which comprise at least one of the compounds according to the present invention, spatially separated, and a mixture of at least two of the compounds according to the present invention. A combinatorial treatment can also be reached by applying either simultaneously or sequentially at least two of the compounds according to the present invention.

The effective compounds to be parenterally administered according to the present invention, preferably intravenous, intramuscular or subcutaneous, all application forms which are known for such application routes are possible, wherein for instance water for injection or
infusion, physiological saline and phosphate-buffered saline in the range of pH 7.0 may be used as excipients, and also all solutions and auxiliary substances which are generally available in the pharmaceutical industry for such purposes.

With respect to oral application forms, for instance in form of tablets, juices, coated tablets (Dragée) or capsules, also all known auxiliary substances and excipients, which are known by the person skilled in the art, can be used. For example, lactose, gelatin, amido1 (diamino phenol hydrochloride), cellulose, waxes, alginic acid, stearic acid or a salt thereof (for example sodium stearate, magnesium stearate), sugar and carbohydrates (for example saccharose, starch, dextrose), pigments (for example yellow orange S, E110) and all substances commonly used in the pharmaceutical industry for such purposes are suitable.

It is preferred if the pharmaceutical composition is in a unit dosage form.

The dosage range to be used for macrolides, is between about 100 mg and 1,500 mg daily, preferably between about 250 mg and 1,000 mg daily, in particular between about 150 mg and 500 mg, most preferably between about 250 mg and 500 mg. Weekly maintenance doses in the range of for instance about 900 mg are very effective, wherein daily doses of for instance between about 100 mg and 250 mg may be applied.

The dosage range to be used with tetracyclines is for instance between about 100 to 1,000 mg/day, in particular 100 to 300 mg/day, preferably between 130 to 180 mg and particularly preferred approximately 150 mg/day. The weekly maintenance doses are ascertained by tests known by the skilled person and should preferably be in the range of about 500 mg.

The doses to be used with gyrase inhibitors are for instance about 100 to 500 mg/day. Weekly maintenance doses in the range of for instance about 800 mg are very effective, wherein daily doses of for instance between about 100 mg and 250 mg may be applied. The acceptable and effective doses for the patient may also be ascertained by experimentation.

The cited dosage ranges do not only depend from clinical aspects (for instance severity, type, duration of the disease, constitution and general health condition of the patient), but also
from the compound to be administered and the respective preparation (oral, parenteral). Further specific instructions for the dosages of the different preparations of the compounds of the present invention are well known to the skilled person and can be gained from literature or ascertained experimentally. The above-mentioned doses can be under-run or exceeded, which depends on the above exemplarily mentioned parameters. Dependent on the patient to be treated and his disease, the medical practitioner will choose the suitable compound, application route, application scheme, dose etc.

In a further embodiment of the present invention, the pharmaceutically acceptable carrier is selected from the group consisting of aqueous solution, injectable solution, delivery system, tablet, film tablet, capsule, drops, ointment, eye ointment, spray, juice and powdered juice.

Combination(s) of anti-migraine agents of this invention can be used for the manufacture of a medicament for simultaneous, separate or sequential use in managing migraine and migraine-related diseases or prophylaxis thereof. The agents can also be used for the manufacture of a medicament for therapy of a disease associated with migraine and cluster headache.

The agents can be administered subcutaneously, intravenously, parenterally, intraperitoneally, intradermally, intramuscularly, topically, enteral (e.g., orally), sublingually, rectally, nasally, buccally, vaginally, by inhalation spray, by drug pump or via an implanted reservoir in dosage formulations containing conventional non-toxic, physiologically acceptable carriers or vehicles. The preferred method of administration is by oral delivery. The form in which it is administered (e.g., syrup, elixir, capsule, tablet, solution, foams, emulsion, gel, sol) will depend in part on the route by which it is administered. For example, for mucosal (e.g., oral mucosa, rectal, intestinal mucosa, bronchial mucosa) administration, via nose drops, aerosols, inhalants, nebulizers, eye drops or suppositories can be used. The compounds and agents of this invention can be administered together with other biologically active agents.

In a specific embodiment, it may be desirable to administer the agents of the invention locally; this may be achieved by, for example, and not by way of limitation, local infusion, topical application, transdermal patches, by injection, by means of a catheter, by means of a
suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes or fibers.

In a specific embodiment when it is desirable to direct the drug to the central nervous system, techniques which can opportunistically open the blood brain barrier for a time adequate to deliver the drug there through can be used. For example, a composition of 5% mannitose and water can be used.

The present invention therefore provides pharmaceutical compositions. Such compositions comprise a therapeutically (or prophylactically) effective amount of the agent or agents, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (e.g., NaCl), alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate, etc.
The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, there are employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g., preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The drug may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, e.g., pressurized air.

The active compounds or agents, like macrolides, tetracyclines and gyrase inhibitors described herein can be formulated as neutral or salt forms. Pharmacologically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.
The amount of agents which will be effective in the treatment of a particular disorder or condition, like the treatment of migraine or migraine-related diseases will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions and/or adjunct therapies of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (e.g., separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in dosages approved by government or federal agencies in standard time courses.

The following examples shall further explain and illustrate the invention, however, they are not supposed to be understood as limiting.
Example 1: Treatment of migraine with macrolides

In a first experiment, the effects of macrolide antibiotics on patients suffering from acute migraine attacks are tested. Tablets are prepared with the help of a commercial tablet-making machine. In table 1, the ingredients of each tablet are summarized. Additionally, for the active compounds (azithromycin, clarithromycin, erythromycin and spiramycin) concentrations per tablet are indicated. The active compound is mixed intimately with the filler/excipient (lactose, starch, cellulose, croscarmellose etc.), the mixture is granulated in customary fashion, dried and the dry granulate is admixed with magnesium stearate. Thereafter, the composition is compressed into tablets. Each tablet contains the concentration of active compound as indicated in table 1. When the tablets are perorally administered to human patients suffering from acute migraine attack 2 times a day (for clarithromycin, erythromycin) or 3 times a day (for spiramycin and azithromycin) for a period of 1 week, acute migraine attacks and cluster-headaches are suppressed effectively. For prophylactic treatment, patients with a history of migraine attacks and cluster-headache, but who are actually without symptoms are treated with 1 tablet per day over a time period of 12 weeks. These patients who normally suffer from acute migraine attacks at least once a month are free of symptoms over the entire period of treatment. Similar results are achieved if two different macrolide compounds are combined for treatment of patients suffering from migraine, cluster-headaches or other forms of paroxysmal headache.

Table 1

<table>
<thead>
<tr>
<th>type</th>
<th>macrolide</th>
<th>macrolide</th>
<th>macrolide</th>
<th>macrolide</th>
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</thead>
<tbody>
<tr>
<td>active compound/tablet</td>
<td>azithromycin</td>
<td>clarithromycin</td>
<td>erythromycin</td>
<td>spiramycin</td>
</tr>
<tr>
<td>concentration of active compound/tablet</td>
<td>262,05 mg azithromycin 2xH2O</td>
<td>723 mg clarithromycin stearat</td>
<td>694 mg erythromycin stearat</td>
<td>244,3 mg spiramycin stearat</td>
</tr>
<tr>
<td>hydromellose</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose</td>
<td>yes</td>
<td></td>
<td></td>
<td>monohydrat</td>
</tr>
<tr>
<td>Ingredient</td>
<td>microcrystalline cellulose</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------</td>
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</tr>
<tr>
<td>starch</td>
<td>corn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sodium croscarmellose</td>
<td>yes</td>
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<td></td>
<td></td>
</tr>
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<td>macrogol</td>
<td></td>
<td></td>
<td>type: 6000</td>
<td></td>
</tr>
<tr>
<td>magnesium hydroxid</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>sodium dodecyl sulfate (SDS)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>povidone</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>polacrilin</td>
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<td></td>
</tr>
<tr>
<td>silicon dioxide</td>
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<td>yes</td>
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</tr>
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<td>pigments</td>
<td>titane oxide (E 171)</td>
<td></td>
<td>chinoline yellow (E104)</td>
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</tr>
<tr>
<td></td>
<td>titane dioxide (E 171)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>talcum</td>
<td></td>
<td>yes</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

**Example 2: Treatment of migraine with tetracyclines**

In a second experiment, the effects of tetracycline antibiotics on patients suffering from acute migraine attacks are tested. Tablets are prepared as generally described in example 1. In table 2, the ingredients of each tablet are summarized. Additionally, for the active compounds (tetracycline, doxycycline, minocycline) concentrations per tablet are indicated. As fillers/excipients saccharose, starch, cellulose and/or behenate are used. Each tablet contains the concentration of active compound as indicated in table 2. When the tablets are perorally administered to human patients suffering from acute migraine attack 3 times a day.
for a period of 1 week, acute migraine attacks and cluster-headaches are suppressed effectively. For prophylactic treatment, patients with a history of migraine attacks and cluster-headache, but who are actually without symptoms are treated with 1 tablet per day over a time period of 12 weeks. These patients who normally suffer from acute migraine attacks at least once a month are free of symptoms over the entire period of treatment. Similar results are achieved if two different tetracycline compounds are combined for treatment of patients suffering from migraine, cluster-headaches or other forms of paroxysmal headache.

Table 2

<table>
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<tr>
<th></th>
<th>tetracycline</th>
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<tbody>
<tr>
<td>type</td>
<td>tetracycline</td>
<td>doxycycline</td>
<td>minocycline</td>
</tr>
<tr>
<td>active compound/tablet</td>
<td>575 mg tetracycline hydrochloride</td>
<td>230.8 mg doxycycline hydrochloride</td>
<td>57.92 mg minocycline hydrochloride 2 H₂O</td>
</tr>
<tr>
<td>concentration of active compound/tablet</td>
<td>500 mg tetracycline</td>
<td>200 mg doxycycline</td>
<td>50 mg minocycline</td>
</tr>
<tr>
<td>calcium behenate</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>saccharose</td>
<td></td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>microcrystalline cellulose</td>
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<td>macrogol</td>
<td>type: 6000</td>
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<td></td>
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<tr>
<td>dimethyl-amino-ethyl-methacrylic acid</td>
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</tr>
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<td>magnesium stearate</td>
<td>yes</td>
<td></td>
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<tr>
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<td>Gelatine</td>
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</tr>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Example 3: Treatment of migraine with gyrase inhibitors**

5 In a third experiment, the effects of gyrase inhibitor antibiotics on patients suffering from acute migraine attacks are tested. Tablets are prepared as generally described in example 1. In table 3, the ingredients of each tablet are summarized. Additionally, for active compounds (ciprofloxacin, ofloxacin, norfloxacin) concentrations per tablet are indicated. In contrast to As fillers/excipients hydromellose, lactose, starch, cellulose and/or carmellose are used.

10 Each tablet contains the concentration of active compound as indicated in table 3. When the tablets are perorally administered to human patients suffering from acute migraine attacks 2-4 times a day for a period of 1-2 weeks, acute migraine attacks and cluster-headaches are suppressed effectively. For prophylactic treatment, patients with a history of migraine attacks and cluster-headache, but who are actually without symptoms are treated with 1 tablet per day over a time period of 12 weeks. These patients who normally suffer from acute migraine attacks at least once a month are free of symptoms over the entire period of treatment. Similar results are achieved if two different gyrase inhibitors are combined for treatment of patients suffering from migraine, cluster-headaches or other forms of paroxysmal headache.
### Table 3

<table>
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<tr>
<th>type</th>
<th>gyrase inhibitor</th>
<th>gyrase inhibitor</th>
<th>gyrase inhibitor</th>
<th>gyrase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>active compound/tablet</td>
<td>ciprofloxacin</td>
<td>ofloxacin</td>
<td>norfloxacin</td>
<td>cinoxacin</td>
</tr>
<tr>
<td>compound/tablet</td>
<td>582 mg</td>
<td>437 mg</td>
<td>490.3 mg</td>
<td>603.2 mg</td>
</tr>
<tr>
<td>active concentration of</td>
<td>ciprofloxacin</td>
<td>ofloxacin</td>
<td>norfloxacin</td>
<td>cinoxacin</td>
</tr>
<tr>
<td>active compound/tablet</td>
<td>500 mg</td>
<td>400 mg</td>
<td>400 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>hydromellose</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lactose</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cellulose</td>
<td>micro</td>
<td>hydroxy-propyl,</td>
<td>yes, + hydroxy-</td>
<td></td>
</tr>
<tr>
<td>crystalline</td>
<td></td>
<td>methyl-hydroxy-propyl</td>
<td>propyl, methyl-</td>
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<td></td>
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<td>corn</td>
<td>poly-O-carboxy-</td>
<td>corn</td>
<td>potato</td>
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<td>methyl + corn</td>
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<td>wax</td>
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<td></td>
<td>171)</td>
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<td>(E171)</td>
<td>oxide (E 171)</td>
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<tr>
<td>talcum</td>
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</tr>
</tbody>
</table>
Example 4.1: Treatment of chronic cluster headache with clarithromycin (Klacid®) – (I)

Patient:
40 years old, male, size 190 cm, weight 85 kg. Chronic cluster headache since four years, which appears in intervals of 6 hours (average duration 30 to 40 minutes).

Symptomatic:
Since one week unilateral, severest headache conditions with attacks every four hours lasting for 30 minutes, day and night and pain maxima peri- and retroorbitally, in the forehead and temporal region.

Medication:
During the first week of the persistent migraine, subcutaneous application of sumatriptan between 12 to 18 mg/day, after day 7 discontinue/stop of sumatriptan medication. The basic medication with methysergid, verapamil and pizotifen was not successful. Thereafter (day 8) oral application of Klacid® (clarithromycin) according to the following scheme: 250 mg/day; maintenance dose 150 mg/day naltrexon for a time period of 10 weeks.

Results:
After the incidence of migraine pains after sumatriptan application an improvement of the pain symptomatic together with decrease of the side effects occurred. In the following night new severe pain attack, from which only light and only preliminary relief could be obtained despite application of 6 mg sumatriptan subcutaneously. During the further sumatriptan medication the pain attacks reoccurred in unchanged periodic during day and increased during night. After the first application of 250 mg Klacid® on the evening of the same day, for the first time a condition free of pain was reached, concurrent with an entire decrease of side effects. The condition free of pain also lasted during the following night. During the entire time of Klacid® medication no new migraine attacks occurred, a condition free of pain was reached and no side effects occurred. The usage of sumatriptan was reduced to 0 mg/day. There was no further medication need for other pain relief drugs.

Due to the structural similarities of macrolides one can certainly conclude that all other compounds which fall in this group show identical or comparable effects. Dependent on the type,
severity and duration of the disease, the health condition of the patient etc. the medical practitioner will choose suitable compound(s) and application forms for the specific patient by repeated experiments. The same is true for the cited compounds of gyrase inhibitors and tetracyclines with the effects according to the invention.

Example 4.2: Treatment of chronic cluster headache with clarithromycin (Klacid®) – (II)

Example 4.1 is repeated with another patient suffering from chronic cluster headaches since years. The headache appears in intervals of about 6 hours, with an average duration of about 30 to 45 minutes. The symptomatic is as described in example 4.1. For therapy, during the first week of persistent migraine, sumatriptan is administered subcutaneously in a dosage range of 12 to 18 mg/day. The basic medication with methysergic, verapamil and pizotifen is successful. On day 8, Klacid® is administered orally in a dose of 250 mg/day for 1 week. The usage of sumatriptan is sequentially reduced to 0 mg/day. After 1 week, Klacid® is administered in a maintenance dose of 150 mg/day for a time period of 10 to 12 weeks. The results are as indicated in example 4.1. During the entire time of Klacid® medication, no new migraine attacks occur. Further, a condition free of pain is reached and no side effects occur. There is no need for other pain relief medication. The patient is successfully treated only with the clarithromycin Klacid®.

Example 4.3: Treatment of chronic cluster headache with clarithromycin (Klacid®) – (III)

Example 4.1 is repeated with still another patient suffering from chronic cluster headaches since years. The headache appears in intervals of about 6 hours, with an average duration of about 30 to 45 minutes. The symptomatic is as described in example 4.1. For therapy, during the first week of persistent migraine, sumatriptan is administered subcutaneously in a dosage range of 12 to 18 mg/day. The basic medication with methysergic, verapamil and pizotifen is successful. On day 8, Klacid® is administered orally in a dose of 250 mg/day for 1 week. The usage of sumatriptan is sequentially reduced to 0 mg/day. After 1 week, the macrolide erythromycin Eryhexal® is administered in a maintenance dose of 120 mg/day for a time period of 10 to 12 weeks. The results are as indicated in example 4.1. During the entire time of Klacid® and Eryhexal® medication, no new migraine attacks occur. Further, a condition free of pain is reached and no side effects occur. There is no need for other pain relief.
medication. The patient is successfully treated with the clarithromycin Klacid® and the erythromycin Eryhexal®.

Example 5: Treatment of migraine with different antibiotics

Example 5.1: Combination of macrolide and tetracycline

In order to investigate the effect of a combination of different antibiotics on patients suffering from migraine and migraine-related diseases, like cluster-headache, a combination therapy is conducted. In a first trial, the macrolide compound azithromycin is used together with the tetracycline doxycycline. Tablets as prepared and described in examples 1-3 are used. The tablets are perorally administered to human patients suffering from acute migraine attacks 2 times a day for a period of 1-2 weeks. Each day, one tablet containing azithromycin and one tablet containing doxycycline is used. Acute migraine attacks and cluster-headaches are suppressed effectively. The effect is prolonged in comparison to the individual application of each individual active compound. For prophylactic treatment, patients with a history of migraine attacks and cluster-headache, but who are actually without symptoms are treated with 1 tablet per day over a time period of 12 weeks. Doxycycline and azithromycin are administered alternatively each day (sequential administration). These patients who normally suffer from acute migraine attacks at least once a month are free of symptoms over the entire period of treatment. Similar results are achieved if doxycycline and azithromycin are administered simultaneously, however, for simultaneously administration only one half of a tablet is used each time, in order to keep the concentrations of active compounds comparable.

Example 5.2: Combination of macrolide and gyrase inhibitor

In a second trial, the macrolide compound erythromycin is used together with the gyrase inhibitor ofloxacin. Tablets as prepared and described in examples 1-3 are used. The tablets are perorally administered to human patients suffering from acute migraine attacks 2 times a day for a period of 1-2 weeks. Each day, one tablet containing erythromycin and one tablet containing ofloxacin are used. Acute migraine attacks and cluster-headaches are suppressed effectively. The effect is prolonged in comparison to the individual application of each
individual active compound. For prophylactic treatment, patients with a history of migraine
attacks and cluster-headache, but who are actually without symptoms are treated with 1
tablet per day over a time period of 12 weeks. Erythromycin and ofloxacine are administered
alternatively each day (sequential administration). These patients who normally suffer from
acute migraine attacks at least once a month are free of symptoms over the entire period of
treatment. Similar results are achieved if erythromycin and ofloxacine are administered
simultaneously, however, for simultaneously administration only one half of a tablet is used
each time, in order to keep the concentrations of active compounds comparable.

Example 5.3: Combination of gyrase inhibitor and tetracycline

In a third trial, the gyrase inhibitor cinoxacin is used together with the tetracycline
minocycline. Tablets as prepared and described in examples 1-3 are used. The tablets are
perorally administered to human patients suffering from acute migraine attacks 2 times a day
for a period of 1-2 weeks. Each day, one tablet containing erythromycin and one tablet
containing ofloxacine are used. Acute migraine attacks and cluster-headaches are suppressed
effectively. The effect is prolonged in comparison to the individual application of each
individual active compound. For prophylactic treatment, patients with a history of migraine
attacks and cluster-headache, but who are actually without symptoms are treated with 1
tablet per day over a time period of 12 weeks. Cinoxacin and minocycline are administered
alternatively each day (sequential administration). These patients who normally suffer from
acute migraine attacks at least once a month are free of symptoms over the entire period of
treatment. Similar results are achieved if cinoxacin and minocycline are administered
simultaneously, however, for simultaneously administration only one half of a tablet is used
each time, in order to keep the concentrations of active compounds comparable.

Example 5.4: Combination of macrolide and gyrase inhibitor and tetracycline

In a fourth trial, macrolide clarithromycin and the gyrase inhibitor ciprofloxacin is used
together with the a tetracycline. Tablets as prepared and described in examples 1-3 are used.
The tablets are perorally administered to human patients suffering from acute migraine
attacks 3 times a day for a period of 1-2 weeks. Each day, one tablet containing
clarithromycin, one tablet containing ciprofloxacin and one tablet containing tetracycline are
used. Acute migraine attacks and cluster-headaches are suppressed effectively. The effect is prolonged in comparison to the individual application of each individual active compound. For prophylactic treatment, patients with a history of migraine attacks and cluster-headache, but who are actually without symptoms are treated with 1 tablet per day over a time period of 12 weeks. Clarithromycin, ciprofloxacin and tetracycline are administered alternatively each day (sequential administration), while on day one clarithromycin, on day two ciprofloxacin and on day three tetracycline is used. These patients who normally suffer from acute migraine attacks at least once a month are free of symptoms over the entire period of treatment. Similar results are achieved if clarithromycin, ciprofloxacin and tetracycline are administered simultaneously, however, for simultaneously administration only one third of a tablet is used each time, in order to keep the concentrations of active compounds comparable.
Claims

1. A use of at least one macrolide compound and/or at least one tetracycline compound and/or at least one gyrase inhibitor, analogs, derivates and/or stereoisomers thereof, pharmaceutically and physiologically harmless acid addition salts and mixtures thereof for the manufacture of a pharmaceutical composition for the prophylactic and/or therapeutic treatment of migraine and/or migraine-related diseases.

2. The use of claim 1, wherein the pharmaceutical composition further comprises a pharmaceutically and physiologically acceptable carrier, auxiliary substance and/or excipient.

3. The use of claim 1 or 2, wherein the macroide compound is selected from the group consisting of azithromycin, clarithromycin, dirithromycin, erythromycin, spiramycin and josamycin and mixtures thereof.

4. The use of claim 1 or 2, wherein the tetracycline compound is selected from the group consisting of tetracycline, oxytetracycline, doxycycline, minocycline, demeclocycline, metacycline and rokitetracycline and mixtures thereof.

5. The use of claim 1 or 2, wherein the gyrase inhibitor is selected from the group consisting of quinolone carboxylic acid, cinoxacin, pipemidic acid, norfloxacin, ciprofloxacin, ofloxacin and enoxacin and mixtures thereof.

6. The use of claim 5, wherein the quinolone carboxylic acid is nalidixic acid.

7. The use of any of the preceding claims, wherein the pharmaceutical composition comprises at least one macrolide compound and at least one tetracycline compound.

8. The use of claim 7, wherein the macrolide compound and the tetracycline compound are applied sequentially or simultaneously.
9. The use of any of the preceding claims, wherein the pharmaceutical composition comprises at least one gyrase inhibitor and at least one macrolide compound and/or at least one tetracycline compounds.

10. The use of claim 9, wherein the gyrase inhibitor and the macrolide compound and/or the tetracycline compound are applied sequentially or simultaneously.

11. The use of any of the preceding claims, wherein the pharmaceutical composition comprises at least two macrolide compounds and/or tetracycline compounds and/or gyrase inhibitors.

12. The use of any of the preceding claims, wherein the pharmaceutical composition is in a unit dosage form.

13. The use of claim 12, wherein the unit dosage form contains the macrolide compound in an amount of about 100 mg to 1,500 mg, preferably 250 mg to 1,000 mg.

14. The use of claim 12, wherein the unit dosage form contains the tetracycline compound in an amount of about 100 to 1,000 mg, preferably 130 to 180 mg.

15. The use of claim 12, wherein unit dosage form contains the gyrase inhibitor in an amount of about 100 to 500 mg.

16. The use of any of the preceding claims, wherein the pharmaceutically acceptable carrier is selected from the group consisting of aqueous solution, injectable solution, delivery system, tablet, film tablet, capsule, drops, ointment, eye ointment, spray, juice and powdered juice.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7048 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of box C.

Note: ""X"" document member of the same patent family

Date of the actual completion of the international search 19 September 2003

Date of mailing of the international search report 09/10/2003

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Authorized officer Borst, M

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<td>DAS P: &quot;Is there an infectious component behind headaches and SIDS?&quot; LANCET, XX, XX, vol. 359, no. 9317, 4 May 2002 (2002-05-04), page 1584 XP004359717 ISSN: 0140-6736</td>
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