Exhibit 9

Concentrated methotrexate solutions

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ABSTRACT

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The invention relates to concentrated methotrexate solutions containing an active substance for the production of a parenterally administered medicament for the treatment of inflammatory autoimmune diseases. The methotrexate is added to a pharmaceutically compatible solvent, in a concentration of more than 25mg/ml. The invention also relates to a ready-made syringe, a carpule containing such a pharmaceutical solution formulation, and a pen injector comprising such a carpule and/or a ready-made syringe.

DESCRIPTION

German

[0001] The present invention relates to concentrated solutions of methotrexate. In particular the present invention relates to the use of methotrexate in the preparation of a medicament to be administered subcutaneously for the treatment of inflammatory autoimmune diseases, wherein the methotrexate is present in a concentration of about 50 mg / ml in a pharmaceutically acceptable solvent.

[0002] The active pharmaceutical ingredient N-{4 - [(2,4-diamino-6-pteridinylmethyl) methyl] benzoyl}-L-glutamic acid (generic name: methotrexate, briefly: MTX) has been known since the early 50s. Methotrexate is a folic acid antagonist. It causes as the antimetabolite Nukleuisäuresynthese intracellular inhibition of dehydrofolate reductase (irreversible binding) with subsequent inhibition of purine synthesis, inhibits LTB $_4$ synthesis in neutrophils, inhibits IL-1 synthesis, suppressed cell-mediated immunity, and inhibits endothelial cell proliferation.

[0003] Methotrexate has been used for a long time due to its preference as a cytostatic effect in oncology. Here it was used in particular for breast cancer, but also for the treatment of children with leukemia. For the latter indication methotrexate is still crucial. Early on was also the efficacy of methotrexate in psoriasis noticed As the psoriasis may be associated with rheumatoid arthritis also own, and this was as a treatment option late 50s first observed in isolated cases.

[0004] Rheumatoid arthritis is usually first treated therapeutically with fast pain relieving and anti-inflammatory substances in the short term. For this purpose, non-steroidal anti-inflammatory drugs (NSAIDs, such as diclofenac) and corticosteroids may be mentioned. However, this does not affect the actual course of the disease. In most patients, NSAIDs and corticosteroids are only so long used to the inflammation and pain subside significantly. Then the dose is often reduced or the drug completely phased out.

[0005] A disease-modifying effect in rheumatoid arthritis. Only the disease modifiying anti rheumatic drugs (DMARD's) As examples of this, also known as "DMARDs" agents with methotrexate may also azathioprine, sulfasalazine, and antimalarial drugs are called. DMARDs directly intervene in the disease process and can slow the disease process, so that a possible early application is desirable. Since rheumatoid arthritis is a chronic disease that DMARDs are usually taking over sufficiently

CLAIMS

1. Use of methotrexate for the production of a medicament to be administered subcutaneously for the treatment of inflammatory autoimmune diseases, wherein the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of about 50 mg/ml.

2. Use according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution, in particular isotonic sodium chloride solution.

3. Use according to any of the preceding claims, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.

4. Use according to claim 3, wherein the inflammatory autoimmune disease is rheumatoid arthritis, in particular juvenile rheumatoid arthritis.

5. Use according to any of the preceding claims, wherein the medicament is present in a form suitable for patient self-administration.

6. Use according to any of the preceding claims, wherein the medicament is contained in an injection device for a single application.

7. Use according to claim 6, wherein the injection device is a ready-made syringe.

8. Use according to any of claims 1 to 5, wherein the medicament is contained in a storage container.

9. Use according to claim 8, wherein the medicament furthermore comprises a preservative.

10. Use according to any of claims 8 or 9, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or

long periods of time, with good efficacy and tolerability of the therapy is often continued for life (long-term continuous therapy), the drug dose can be adapted to the disease process.

[0006] In contrast to chemotherapy in cancer patients is methotrexate. As a basic therapeutic for the treatment of rheumatoid arthritis is many times, sometimes up to 1000-fold dose low, so we also speak at the antirheumatic therapy of the "low-dose methotrexate therapy" The antirheumatic therapy in Germany, a dose range of 5.0 to 30.0 mg per week is common in other European countries is dosed up to 40.0 mg per week. It is very important that methotrexate is only given once a week.

[0007] The application of methotrexate can in principle be as orally and parenterally. However, the first orally via tablets for a long time was therapy was replaced by parenteral formulations, since it has been established that methotrexate is absorbed from tablets unreliable and therefore no sufficient accuracy is ensured with the dose-dependent therapy. Suitable for parenteral administration are usually cytotoxic drugs prepared by dissolving the active ingredient in a suitable solvent, for each individual patient by using a specific amount of active ingredient. The handling of cytotoxic drugs and the formulation containing cytostatic drugs is not without problems and the legislature provided with strict conditions. For example, cytotoxic drugs may carry out a suitable and specially created for this extraction system is not prepared. As rheumatologists and primary care physicians have usually do not have such facilities, it is not permitted to methotrexate making facilities, where already the rearing of a syringe from a bottle (for example, a piercing surface, which contains the active ingredient solution) is seen as preparation.

[0008] For this reason, pre-filled syringes are designed to eliminate the step of winding. First corresponding pre-filled syringes for subcutaneous administration for the present applicant has been approved throughout Europe. With these pre-filled syringes, the application by the physician, medical personnel or, in the self-application, it is possible by the patient himself without the need of an intermediate pharmacist needs, which has a suitable discharge system.

[0009] Known from the prior art in relation to the treatment of rheumatoid arthritis syringes for parenteral administration are solutions containing methotrexate, in which the active ingredient in a concentration of up to 25mg/ml in a pharmaceutically acceptable solvent is present (trade names: Lantarel ® from Wyeth, Metex ® of the applicant), the injection solution Lantarel ® concentration of 25 mg / ml (trade name: Lantarel ® FS is 25mg) not approved for subcutaneous administration. Methotrexate has become the "gold standard" developed in the treatment of rheumatoid arthritis

[0010] The subcutaneous administration of methotrexate for the treatment of rheumatoid arthritis, but also with maximum concentrations of 25 mg / ml, is further described in Jansen et al, Pharmaceutisch Weekblad, Year 1999, Volume 134, No. 46, pp. 1592 -. 1596 Kurnik et . al, Alimentary Pharmacology & Therapeutics, born 2003, Volume 18, No. 1, pp. 57 -. 63 Zackheim et al, Journal of the American Academy of Dermatology, Year 1992 26, No. 6, page 1008

[0011] As already described, it is necessary for successful treatment with methotrexate basis that the rheumatoid arthritis patients over a long period, sometimes a life - long, the appropriate dose weekly methotrexate is administered. For parenteral administration, the described speaks against the oral administration route favorable bioavailability. Furthermore, children in particular have a certain aversion to taking pills. However it has been found that precisely the subcutaneous administration is associated with difficulties. In therapies with those known in the prior art preparations turned out to a negative attitude on the part of patients. This is due to the problem, in the weekly

a carpule.

11. Use according to claim 10, wherein the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device, in particular a pen injector.

12. Use according to claim 11, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.

13. Use according to claim 7, wherein the ready-made syringe contains a dosage of 5 to 40 mg, in particular 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.

14. Use according to any of claims 7 or 13, wherein the ready-made syringe is constructed such that it allows patient self-administration by a patient with limited fine motor skills.

15. Methotrexate for use in the treatment of inflammatory autoimmune diseases, wherein the methotrexate is to be administered subcutaneously and the methotrexate is present in a pharmaceutically acceptable solvent at a concentration of about 50 mg/ml.

16. Methotrexate for use according to claim 15, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution, in particular isotonic sodium chloride solution.

17. Methotrexate for use according to any of claims 15 or 16, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, bronchial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.

18. Methotrexate for use according to claim 17, wherein the inflammatory autoimmune disease is rheumatoid arthritis, in particular juvenile rheumatoid arthritis.

19. Methotrexate for use according to any of claims 15 to 18, wherein the methotrexate is present in a form suitable for patient self-administration.

20. Methotrexate for use according to any of claims 15 to 19, wherein the methotrexate is contained in an injection device for a single application.

21. Methotrexate for use according to claim 20, wherein the injection device is a ready-made syringe.

22. Methotrexate for use according to any of claims 15 to 19, wherein the methotrexate is contained in a storage container.

23. Methotrexate for use according to claim 22, wherein the methotrexate-containing solvent furthermore comprises a preservative.

24. Methotrexate for use according to any of claims 22 or 23, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.

25. Methotrexate for use according to claim 24, wherein the storage container is a carpule and wherein said carpule is suitable for administering the methotrexate by means of an injection device

time interval required relatively large quantities can lead to drug solution (eg with appropriate drug dose up to 3 ml) under the skin, which is particularly inbegriffren children, the weekly visit to the doctor is not easy to convey.

[0012] There is therefore a need for pharmaceutical formulations of methotrexate, which may allow the patient, including children, as simple and painless with good bioavailability over a long period are administered regularly, especially a week, and thus a high "patient compliance" leads. Advantageously, the patient can self administer the pharmaceutical formulation.

[0013] The present invention is thus based on the object to provide a pharmaceutical preparation for the treatment of inflammatory autoimmune diseases, especially rheumatoid arthritis, provide, which overcomes the above-described drawbacks of the known in the prior art preparations.

[0014] The problem underlying the present invention is achieved by the object of the appended claims.

[0015] In a first embodiment, the invention provides the use of methotrexate to be administered subcutaneously for preparing a medicament for the treatment of inflammatory autoimmune diseases, wherein the methotrexate is present in a concentration of about 50mg/ml in a pharmaceutically acceptable solvent, ready.

[0016] In a further embodiment, the invention Methotrexate for use in the treatment of inflammatory autoimmune diseases is prepared, wherein the methotrexate is to be administered subcutaneously in a concentration of about 50mg/ml is in a pharmaceutically acceptable solvent.

[0017] According to the present invention, drugs or pharmaceutical Lösunssformulierungen are provided which include methotrexate at a concentration of about 50mg/ml in a pharmaceutically acceptable solvent.

[0018] As the pharmaceutically acceptable solvents according to the invention can be considered in all solvents, which are pharmaceutically acceptable and not with the active ingredient and any other ingredients of the drug or the pharmaceutical solution formulation are incompatible. According to the invention are particularly suitable pharmaceutically acceptable solvent is water, in particular water, for injections, as well as water comprising isotonization additives and sodium chloride solution, in particular isotonic sodium chloride solution. Most preferably, water for injections. As exemplary isotonization, soluble salts (sodium chloride, potassium chloride), sugars (glucose, lactose), sugar alcohols (mannitol, sorbitol), and combinations of these excipients may be used in the invention.

[0019] Addition, the inventive drug can Isotonierungszusätzen also in the art of pharmaceutical solution formulations contain conventional additives. In particular, the inventive medicament may contain conventional excipients with the following functionality: Eu / Isohydrisierung (acetate, phosphate, citrate buffer), antioxidants (ascorbic acid, usual in the art of sulfur compounds) Läsungsvermittlung (complexing agents, solubilizers, cosolvents eg cyclodextrins, polyvidone, polysorbates, lecithin, glycocholate), increase in viscosity, pH adjusters (acids, bases, or acidic or basic salts). In a particularly preferred embodiment, the pH of the inventive medicament is between 7.5 and 9

[0020] The novel drugs are directed to the treatment of inflammatory autoimmune diseases. The term "inflammatory autoimmune disease" encompasses all inflammatory autoimmune diseases, which can be treated with methotrexate useful. As examples of inflammatory autoimmune diseases, which can be treated with the inventive drug can rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, ulcerative colitis, asthma, Alzheimer's disease, multiple sclerosis, ankylosing spondylitis, joint arthroses, or psoriasis, and psoriasis arthritis and psoriasis vulgaris in particular called plaque-type. Particularly preferably the invention are suitable drugs for the treatment of rheumatoid arthritis, including juvenile arthritis, especially as the oligoarthritische and polyarthritische form of juvenile arthritis.

[0021] The administration of the drug subcutaneously. In particular, the application of medications by injection subcutaneously. Furthermore, it is preferred that the medicament is in a form that makes it possible that the subcutaneous administration of the drug by the patient itself is made (self-administration). Such treatment of subcutaneous self-administration has proved, for example, the administration of insulin through the affected diabetics itself and leads to a high treatment acceptability by the patient ("patient compliance"). In the case of rheumatism in self-application can also be dispensed to the usually weekly successful doctor's visit.

[0022] In a preferred Ausführungsförm the present invention, the inventive medicament is in an injection device for a single application, in particular a pre-filled syringe containing. Under an injection device for a single application according to the invention, a device is to be understood that. Alongside a container which contains the pharmaceutical solution formulation according to the invention, an injection needle (cannula), wherein by this the medicament can be administered to the patient Further comprising an injection device such a mechanical arrangement (such as a punch or a flexible bladder) with the aid of the drug can be forced through the needle from the container. Such an injection device for a single application is further characterized in that it contains a desired single dosage of the drug and thus the application, the container, which contains the pharmaceutical solution formulation according to the invention, is to be emptied completely, in order to give the intended dosage. Because of this fact, according to the

in particular a pen injector.

26. Methotrexate for use according to claim 25, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.

27. Methotrexate for use according to claim 21, wherein the ready-made syringe contains a dosage of 5 to 40 mg, in particular 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg, of methotrexate.

28. Methotrexate for use according to any of claims 21 or 27, wherein the ready-made syringe is constructed such that it allows patient self-administration by a patient with limited fine motor skills.

above embodiment, as a rule is not necessary to blend a preservative to the pharmaceutical solution formulation of methotrexate.

[0023] In a novel injection device for a single application is preferably a dose of the drug methotrexate 5mg to 40mg, included. Particularly preferably comprises an injection device for a single application of the invention, a dose of 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27 , 5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg. An obligation to provide a particular desired dosage required volume of liquid contained in the injection device for a single application needs to be depends on the chosen concentration of the drug solution and opens up to the person skilled in a simple way. Thus to provide a dose of active substance of 30.0 mg in an inventive concentration of methotrexate in the pharmaceutically acceptable solvent of 50mg/ml should an injection device for a single application contain a liquid volume of 0.6 ml.

[0024] A particularly preferred embodiment of an inventive injection device for a single application is a prefilled syringe. Syringes are on the pharmaceutical techniques well known, especially in the field of treatment of rheumatoid arthritis with methotrexate. On the German market already pre-filled syringes are distributed containing methotrexate solutions with concentrations of 7.5 mg / ml, 10.0 mg / ml and 25mg/ml (trade name: Lantarel ® from Wyeth, Metex ® of the applicant, with the commercial product Lantarel ®) FS 25 mg is not approved for subcutaneous administration). Application approved preparations of the prior art have the disadvantage that, depending on the week to be administered amount of drug, relatively large quantities of fluid under - although the provision of methotrexate solutions in prefilled syringe, sometimes for Seibstapplikation, patient compliance positively influenced the Subcutaneous have the patient's skin must be brought. At a dose of 30mg drug usual weekly means that the currently most concentrated drug solution of prior art for the subcutaneous administration, namely 10mg/ml (commercially product Metex ® 10mg/ml of the applicant), a volume of 3 ml to be injected under the skin must . This high amount of liquid is the patients, especially children, sometimes difficult to explain what leads to reduced patient compliance.

[0025] According to the invention provided drugs contain the active ingredient on the other hand, highly concentrated solutions methotrexate, and reduce the amount of liquid to be administered at a given dose of active ingredient weekly. For example, it would therefore be at the concentration of the present invention to observe a weekly 50mg/ml active dose of 30 mg is sufficient to administer a liquid volume of only 0.6 ml subcutaneously. It can be expected that this will have a positive impact on patient compliance.

[0026] Syringes are on the pharmaceutical arts are well known and are not according to the invention particularly limited. Invention include pre-filled syringes, for example, disposable injection systems such as the Uniject ® injection system. In one embodiment, the syringe can already be provided with a suitable needle for subcutaneous injection, in an alternative embodiment, the syringe is initially provided with a rubber cap or the like, which, prior to the application by the physician, the medical staff or in subcutaneous self-administration is replaced by the patient himself by a separately packaged sterile cannula.

[0027] Preferably the inventive syringe is designed so that it is suitable for subcutaneous administration of the drug solution, which can be accomplished in particular by providing for a suitable hypodermic needle. In a more preferred embodiment, the syringe is designed in such a way that even patients with rheumatoid arthritis who have limited manual fine motor skills and therefore not exclusively be able to inject himself a drug with conventional design syringes, can perform a self-application. These preferably have particular stamp and back stopping constructed and sized so that the rheumatic patient handling is facilitated. Such enriched syringes are named in the art.

[0028] In a further preferred embodiment of the present invention, the inventive medicament is contained in a storage vessel. Under a storage vessel according to the invention any conventional in the art, the container is to be understood, in which / wherein the medicament or the pharmaceutical solution formulation of the invention properly, ie, in particular sterile, can be sensed and stored. As examples of supply vessel in the sense of the invention, a vial, a vial one bag, a glass ampoule, or a carpule may be cited. According to an embodiment of the invention must for application of the medicament to the patient, first, the desired amount of pharmaceutical solution formulation by means of an injection device (for example, a conventional disposable syringe) from the reservoir (such as a vial) are removed, whereas in an alternate embodiment of the invention the pharmaceutical solution formulation means of an injection device (such as a pen injector) directly from the supply vessel (for example, a carpule) can be applied.

[0029] In a preferred embodiment of the invention the storage vessel includes the drug methotrexate, which is dissolved in the pharmaceutically acceptable solvent, at least not a preservative. The preservative used in this invention is not particularly restricted, and a skilled artisan will readily be able, from the known preservatives for pharmaceutical purposes, a select suitable. Preferred preservatives are cresols, benzyl alcohols, Phenylethylalkohole called. The preservative is used in particular to the case of partial removal of the drug (for example, by a conventional disposable syringe or a pen-type injector), in a storage vessel according to the invention (for example, a vial or a carpule) preserve remaining pharmaceutical solution formulation.

[0030] The total dosage amount of the drug methotrexate in a storage vessel according to the invention is not particularly limited and in particular by the dimensions of the Voratsgefäßes and thus from the fluid volume is determined, which can hold the reservoir. Preferably, an inventive storage vessel a total dosage amount of from 5 to 5000 mg methotrexate.

[0031] A preferred example of a storage vessel, in which the inventive medicament is contained, a carpule may be cited.

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