

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19358 A2

- (51) International Patent Classification⁷: **A61K 31/00** (74) Agent: **HARRISON GODDARD FOOTE**; Tower House, Merrion Way, Leeds LS2 8PA (GB).
- (21) International Application Number: **PCT/EP00/08879**
- (22) International Filing Date:
8 September 2000 (08.09.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
A 1558/99 10 September 1999 (10.09.1999) AT
60/183,806 22 February 2000 (22.02.2000) US
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- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— *Without international search report and to be republished upon receipt of that report.*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 01/19358 A2

(54) Title: **PHARMACEUTICAL COMPOSITIONS FOR TREATING PSORIASIS**

(57) Abstract: The use for the manufacture of a medicament for treating psoriasis of dexrazoxane, the d-isomer of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane, or a physiologically acceptable salt thereof.

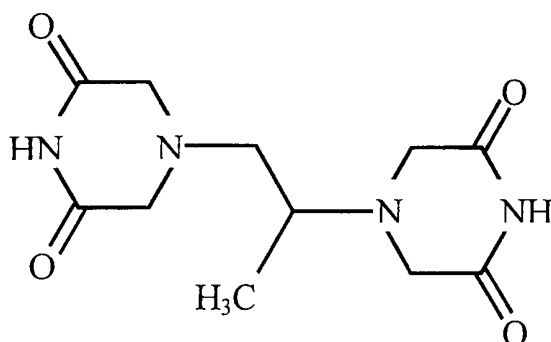
PHARMACEUTICAL COMPOSITIONS FOR TREATING PSORIASIS

This invention relates to pharmaceutical compositions based on 1,2-bis(3,5-dioxopiperazin-1-yl)-propane and pharmaceutically acceptable salts thereof.

5

1,2-bis(3,5-dioxopiperazin-1-yl)-propane is of formula

10



15 and it may exist in the d-isomeric form, the l-isomeric form and in the racemic dl-form.

The racemic dl-form of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane is known as razoxane. Compounds of this kind belong to the family of bis-dioxopiperazines, which have been known for a long time, particularly as anti-tumor agents. This class of compounds, their use and preparation are described in, e.g. GB-A-1 234 935, GB-A-1 374 979, US-A-4 275 063, EP-A1 491 053, EP-A1 256 137, EP-A1 230 474, EP-A2 014 327 and EP-A1 125 475.

25 The bis-dioxopiperazines represent lipophilic derivatives of EDTA (ethylene diamino tetraacetic acid), a substance known as a chelating agent. As such they are thought to act by chelating iron, thereby reducing site-specific oxygen radical production. The bis-dioxopiperazines exert topoisomerase II inhibitory activity which presumably is responsible for the antitumor activity of these drugs. The d-enantiomer of razoxane is known as dexrazoxane. The current clinical use of dexrazoxane is to prevent doxorubicin-induced cardiac disease in patients with metastatic breast cancer.

30

Dexrazoxane is commercially available as the hydrochloride salt. In Europe, dexrazoxane.HCl is available from Chiron, Inc under the registered trade mark Cardioxane, whilst in the US it is available from Pharmacia Upjohn under the registered trade mark Zinecard. A discussion of the chemical, biological and clinical aspects of dexrazoxane and other bis-dioxopiperazines can be found in *Current Medicinal Chemistry* (1998) 5, 1-28. GB-A-1 234 935 is one of the oldest publications on bis-dioxopiperazines and describes their preparation through cyclisation of the corresponding tetracarboxamidomethyl derivatives through heating together with polyphosphoric acid. The therapeutic spectrum of these drugs includes certain forms of cancer, including leukaemia, and certain non-malignant forms of proliferative disease.

For the preparation of dexrazoxane mainly two methods have been described (US 3 941 790). In the first method 1,2-diaminopropane tetraacetic acid and formamide are heated together to yield the cyclic product. In the second method the corresponding tetraamide of the above tetraacid is heated in polyphosphoric acid or phenol, also leading to cyclisation of the compound (see the previously mentioned GB-A-1 234 935).

Other methods for preparation of dexrazoxane are known, e.g. described in US Pat. No. 4 764 614 or EP-A-0 330 381.

The preparation of a lyophilised composition containing dexrazoxane that is stable and less light-sensitive is described in detail in US Pat. No. 5 760 039.

Psoriasis is a chronic skin disease characterised by scaling and inflammation. The cause of psoriasis is unknown but recent research indicates that it is likely to be an autoimmune disease. Psoriasis is a serious and unpleasant condition which has no cure and not all treatments work for each individual.

- Psoriasis can be very painful, but the pain is more than skin deep. The emotions suffer as well. It presents people with physical limitations, disfiguration, and its tedious daily care always demands too much time. Embarrassment, frustration, fear and depression are common. In extreme cases, a loss of self-esteem results in a complete withdrawal from society. Various kinds of temporary relief are available and they work with varying degrees of success. Treatments and medications are often time consuming and expensive but one thing is certain: the symptoms may come and go, but they almost always come again. It is a lifelong disease.
- Psoriasis is treated using what is sometimes called the "1-2-3" approach. Step 1 is topical treatment, step 2 is phototherapy and step 3 is systemic treatment. Medicines currently prescribed for systemic treatment are the immunosuppressants methotrexate and cyclosporine A, hydroxyurea and retinoids.
- Methotrexate and cyclosporine A have unpleasant and potentially dangerous side effects. Moreover, all these treatments leave patients with recurrent psoriasis and because different patients respond differently to varying treatments, it would be very welcome to have additional weapons in the therapeutic armoury.
- In 1976, D.J. Atherton (*Lancet*, ii, 1296, 1976) for the first time proposed the use of racemic razoxane (ICRF-159) for the treatment of psoriasis. A review on the therapeutic use of razoxane in psoriasis can be found in the *British Journal of Dermatology* (1980) 102, 307. The drug had relatively good efficacy and good tolerability, but some unpleasant side effects and certain toxicities were noticed.
- Therefore administration of the drug was recommended only under strictly controlled conditions. Horton and Wells (*British Journal of Dermatology* (1983) 109, 669-673) again reported the relatively good success of treatment with razoxane, however, a considerable proportion of patients stopped treatment because of relatively severe side effects. The most frequently seen side effect was neutropenia, a potentially fatal depletion of neutrophils (a subset of leukocytes), which was reported to occur in a number of patients even on low doses insufficient to control psoriasis. Other side

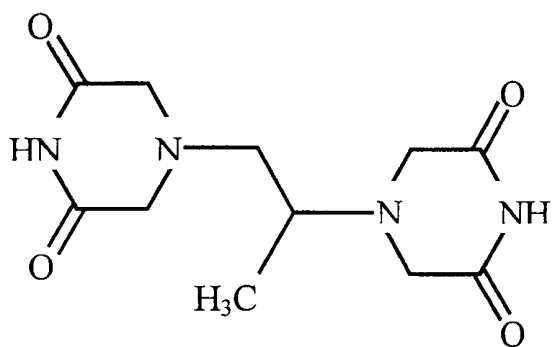
effects were alopecia, nausea, diarrhoea, nasal bleeding, leg ulceration, lethargy, headaches and squamous epitheliomata.

Because of this and further complications arising after chronic administration, razoxane was not developed further and today is not recommended for treatment of psoriasis. Hitherto, therefore, the known facts about razoxane have been that it cannot be used both safely and effectively to treat psoriasis.

Surprisingly, it has now been demonstrated that the d-enantiomer of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane, dexrazoxane, by itself can be used to treat psoriasis safely and effectively. Indeed, our studies indicate that the treatment results are truly remarkable for some patients, with relief from refractory psoriasis for periods of up to at least one year. No serious side effects have been reported in clinical trials to date, with the vast majority of patients being free of neutropenia and no recorded cases of vomiting, nausea or diarrhoea.

According to the present invention a new pharmaceutical composition for treatment of psoriasis contains as active compound dexrazoxane, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier and/or excipient.

The invention also includes a method of treating psoriasis in a patient, comprising administering to the patient a therapeutically effective amount of dexrazoxane, the d-isomer of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane, a compound of formula



or a physiologically acceptable salt thereof.

The invention is further described below with reference to accompanying figure 1, which is a graphical presentation of the mean value (n=7) of the Psoriasis Area and
5 Severity Index (PASI) over a treatment protocol having three dexrazoxane administration cycles.

The method may comprise administering the dexrazoxane by injection or infusion (or by other internal administration route, for example oral) at a daily dosage of, for
10 example, between 250mg and 1750mg, and in one suitable protocol comprises administering the dexrazoxane at increasing dosages, for example at a first daily dosage for an initial period of up to e.g. 5 days, a second daily dosage for a second period of up to e.g. 5 days and a third daily dosage for a third period of up to e.g. five days. The initial, second and third periods may be spaced apart and preferably are
15 one or two days long; one of the initial, second and third periods is dispensed with in some treatment protocols. For an adult, the first daily dosage is usually from about 250mg to about 750mg (e.g. about 500mg), the second daily dosage is usually from about 750mg to 1250mg (e.g. about 1000mg), and the third daily dosage is usually from about 1250mg to 1750mg (e.g. about 1500mg).

20

In any event, the most preferred protocols for internally, e.g. parenterally, administering dexrazoxane involve administering the dexrazoxane at intervals, for example with an interval between administration periods of from 5 to 20 days, more usually from 8 to 16 days and most preferably of from 10 to 14 days, e.g. 12 days.
25 As already indicated, an administration period may last two successive days, on each of which dexrazoxane is administered. Alternatively single day administration periods may be used, or administration periods of more than two days, in which case dexrazoxane may be administered on all of the days or only some of them. Particularly preferred protocols consist of three spaced administration periods, for
30 example of two days in length and/or separated by intervals of 12 days; thus a protocol may consist of the three cycles appearing in Figure 1. The administration

protocol may be repeated as necessary, for example after a period of between a month and a year or more. The parenteral administration is suitably by infusion or injection and the dexrazoxane is usually (but not exclusively) administered in the form of a salt.

5

The dosage may be varied, for example increased, over the course of the treatment. In particular, the dosage may be increased after the first administration period of the protocol described in the previous paragraph if the patient's initial response is not adequate. Conveniently, an adult is administered a dose of from about 250mg to about 750mg on each day of an initial two day administration period, after which the dose may be maintained or increased (e.g. to about 750mg to about 1250 mg). After the second administration period, the dosage may be maintained or, if necessary increased (or even decreased) for the third administration period. The dosage is conveniently, but not necessarily, altered in steps of 500mg.

15

The dexrazoxane weights and weight percentages specified in this application refer to dexrazoxane hydrochloride, i.e. they relate to dexrazoxane as the hydrochloride salt. If an alternative form is used appropriate adjustments should be made on the basis of the relative molecular weights of the two forms. Similarly, dosages must be suitably adjusted for the treatment of children.

20

In one class of methods, therefore, the dexrazoxane is administered intravenously or otherwise by injection or infusion. In current practice, the solutions for injection or infusion are made by reconstituting lyophilised dexrazoxane just prior to administration. The lyophilisate may be packaged in an amount corresponding to the unit dosage to be used and packages containing about 250mg, from about 750 mg to about 1250 mg or about 1250 mg to about 1750 mg are each included in the invention. The invention also includes the use of dexrazoxane to manufacture liquid dexrazoxane preparations in ready to use form, and the administration of such ready to use liquid formulations (solutions).

25

30

In another class of methods the dexrazoxane is administered topically, transdermally or percutaneously, e.g. in the form of an ointment, lotion or plaster. Other methods comprise the oral administration of the dexrazoxane, for example in tablet form. The dexrazoxane may be administered in the form of a suppository. Alternatively the
5 dexrazoxane is administered as a topical formulation, for example as an ointment, cream or gel. The concentration of dexrazoxane is not critical. However, some topical formulations contain at least 0.1 wt % dexrazoxane, and more usually contain from 0.25 wt % and especially 0.5 wt % to 5 wt % or more dexrazoxane. One class of formulations contains 1-2 wt % of dexrazoxane. The invention includes
10 formulations adapted for topical administration to the exclusion of oral or parenteral administration or administration by injection or infusion. The topical formulations are suitably packaged in tubes of up to 100g, associated with instructions to use them to treat psoriasis.

15 The topical formulations may by way of example contain conventional carriers. By way of non-limiting example, the ointments may contain water and one or more hydrophobic carriers selected from liquid paraffin, polyoxyethylene alkyl ether, propylene glycol and white vaseline. The carrier compositions of the creams are typically based on water and white vaseline, in combination with glycerol and more
20 minor components, e.g. one or more of glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. The gels may by way of example be formulated using isopropyl alcohol and water, suitably in combination with minor components, for example one or more of glycerol and hydroxyethyl cellulose.

25 The dexrazoxane may be used in combination therapy, for example with a non-steroidal anti-inflammatory drug, a TNF inhibitor or a vitamin. The invention therefore includes products, especially comprising a topical formulation, containing dexrazoxane and an agent useful for treating psoriasis or relieving its symptoms as a combined preparation for simultaneous, separate or sequential use in treating
30 psoriasis. The product may be a topical formulation containing the two or more active agents in combination.

During a clinical trial a rapid amelioration of disease-associated signs was seen even in particularly resistant cases that had a long history of psoriasis. The itch diminished several hours after the first administration and it practically disappeared after the next
5 dose. The scaling was reduced, the madescence disappeared, the thickness of the affected area was significantly reduced and the patients were free of arthralgia.

The patients showed marked subjective and objective responses as a 25-30% regression of the skin lesions, without experiencing the known side effects of
10 razoxane.

The preferred formulation is a sterile solution for injection or infusion, but ointments, lotions, oral forms, plasters and suppositories may also be employed.

15 The invention is illustrated in the following examples:

Clinical trials to demonstrate the efficacy of dexrazoxane:

20 EXAMPLE 1

This patient, a 55 year old male, had a 20 year history of psoriasis. The disease started after mental stress (loss of near person) with a rash on the hairy part of the head. From the very onset of the disease the patient received intensive treatment with
25 vitamins B₁₂, B₆, B₂, and calcium. He had artificial hyperthermia with pyrogenal injections, methotrexate, various ointments (e.g. salicylic ointment) under a dermatologist's observation at a specialised clinic. In spite of the treatment the psoriatic rash was spreading over the trunk, upper and lower extremities and it was accompanied by a marked general itch. The patient had practically no remissions.
30 Concurrent diseases were grade II hypertension and chronic cholecystopancreatitis.

At the first examination the patient complained about itching all over the body (resulting in insomnia) and pain in the large joints (mainly knees). The skin on the back, buttocks, chest and arms was covered with a erythematous papular and pustular rash with a white coating (desquamation). A similar though less intense rash was
5 seen on the legs. The patient's general status, the haematological and biochemical profiles were within normal.

On the first and the second day of the treatment cycle the patient received the first doses of Cardioxane® (dexrazoxane.HCl) at 500mg each day by intravenous drip
10 infusion. On day 15 the patient reported of the amelioration of itch several hours after the first Cardioxane® administration. The itch practically disappeared after the next dose of Cardioxane® therapy at 1000mg on day 16. The patient presented with amelioration of scaling, disappearance of madescence, amelioration of hypernia and flattening of rash, and complete disappearance of arthralgia. The patient slept well for
15 the first time in a long disease period. The effect was still preserved at the examination on day 29 and day 30 when the patient was given the last two injections of Cardioxane® at 1500mg each.

At the last examination on day 29 the patient presented with flattening of the rash,
20 disappearance of some lesions and appearance of normal skin areas (up to 2cm in diameter, especially on the lower limbs). A total reduction by 25%-30% of total skin lesions was diagnosed. The itch, although returning briefly approx. 1.5 weeks after the first two injections, did not re-appear after the 3rd and 4th injections, nor did arthralgia. There were no adverse events after any of the injections.

25

EXAMPLE 2

This patient, a 50 year old male, had suffered from generalised psoriasis for 25 years. The rash first appeared on the head and the right upper limb to spread over the trunk
30 and upper limbs later. The patient had received therapies similar to the patient described in Example 1. In addition he received UV therapy, peloids, sulfurated

hydrogen baths, but without lasting effect. The patient had no concurrent illness except asthenia, sinus arrhythmia and left ventricular hypertrophy. The skin on the back, lumbar region and shoulders was covered with merged erythematous papular, bullar and desquamating lesions. The rash on the lateral chest walls and on the lower limbs was mainly erythematous and less marked. The skin lesions covered about 50% of the body surface. The patient did not complain of itch.

The patient was given 6 intravenous drip injections with Cardioxane® according to the following schedule:

10

On day 1 and day 2 each 500mg Cardioxane®,
on day 15 and day 16 each 1000mg Cardioxane®,
and on day 29 and day 30 each 1500mg Cardioxane®.

At examination on day 15 and day 29 the patient presented with a mild amelioration of erythema on the back. The remaining lesions demonstrated no change. There were no side effects.

20 EXAMPLE 3

This patient, a 37 year old female, had a 16 year history of the disease, manifesting itself after an abortion and mental stress. The psoriatic rash appeared on the hairy part of the head and neck to spread further over the body. The patient received insolation with but a temporary effect. The patient had had 4 hospitalisations to receive therapy with vitamins, calcium, and various ointments. After a period of intense stress due to the loss of a close person the patient had a sharp exacerbation of the disease, with erythematous lesions covering most of the body. The patient also had a history of periodic episodes of allergic asthmatic bronchitis.

30

At the first examination on day 1 the patient presented with continuous erythematous papular psoriatic rash with desquamation on the front abdominal wall (below the submammary fold), the inguioileac, the lumbosacral, the gluteal regions and the lower limbs, severe itch, and scraping tubular breathing (asthmatic bronchitis). Of note was
5 also a marked increase in the eosinophile count.

The patient received 6 intravenous drip injections of Cardioxane® according to the protocol given in Example 2. At examination on day 15 the patient reported the complete disappearance of skin itch at 2 or 3 days after the first injection of
10 Cardioxane®. The lower half of the abdomen as well as the upper gluteal quadrants were practically free of rash. There were no adverse events after the injections of Cardioxane®, except a mild pain along the vein path at the injection site.

At the examination on day 30 the patient presented with complete regression of about
15 80% of the rash, with residual depigmentation in the lumbosacral region and on the legs. The itch was still absent. No adverse events were reported, despite the concurrent allergic status of the patient.

20 EXAMPLE 4

The efficacy and tolerability of dexrazoxane in patients with refractory psoriasis was assessed in a clinical study.

25

After screening, eligible patients received 500mg of Cardioxane® by intravenous infusion on each of two consecutive days. They were reviewed 7 and 14 days after the first day of treatment. The patients received the second cycle of treatment, which consisted of either 500mg Cardioxane® by intravenous infusion, on each of two
30 consecutive days (days 15 and 16, in this case), if a complete response had occurred,

or 1000mg Cardioxane[®] by intravenous infusion, on each of two consecutive days (days 15 and 16, in this case), if an incomplete response had occurred.

5 A third cycle of treatment was given after the same interval (days 29 and 30, in this case). Patients who showed a complete response received the same dose as they received in the second cycle, whilst one patient, who showed no response, received two doses of 1500mg.

10 The primary efficacy parameter was the percentage reduction in skin area and severity affected by psoriasis, as determined by the standardised assessment of the Psoriasis Area and Severity Index (PASI).

15 Seven patients have been enrolled in the study and all patients have completed a follow-up period of two weeks. At the beginning of the treatment, the PASI-scores ranged between 23.1 and 44.1, with a mean score of 31.9. Most of the patients did respond to the treatment, except for one patient, who was absolutely resistant to therapy. At the end of the third treatment cycle, the PASI-scores ranged between 3.4 and 29.7, with a mean score of 11.4.

20 At 11 weeks after the start of the therapy, the mean reduction in PASI was 65%, with a maximum reduction of 88%, and one resistant case. The tolerability of the treatment was excellent, and no serious adverse events were reported. In addition, the therapy with Cardioxane[®] resulted in better and faster relief of symptoms associated with psoriatic arthritis, when compared to treatment with cyclosporine A (which is
25 the standard treatment in this indication and had been used previously in the clinic).

The results are shown in Table 1 and represented graphically in Figure 1.

TABLE 1: **The effect of Cardioxane[®] treatment on the Psoriasis Area and Severity Index (PASI)**

PASI score and patient number / initial							
visit No	1 / HH	2 / MR	3 / MZ	4 / PH	5 / PZ	6 / FJ	7 / DJ
v1	23.1	43.6	29.8	27.0	29.1	44.1	26.6
v4	11.3	36.3	18.4	18.6	16.9	24.8	23.6
v7	7.7	23.1	11.6	13.5	9.9	20.3	23.0
v9	6.5	15.6	9.7	10.8	9.3	15.6	21.8
v10	6.5	12.3	7.1	12.0	7.8	15.6	28.5
v11	5.6	14.0	6.5	5.2	3.4	15.3	29.7

mean PASI score at the start of treatment (n=7): $\bar{x} = 31.9$

mean PASI score after 7 weeks (n = 7): $\bar{x} = 11.4$

5 mean reduction in PASI score (n = 7): 65%

Of 7 patients treated, only one was diagnosed with mild, reversible leukopenia (approximately 3×10^9 cells per liter, it was classified as grade I toxicity according to World Health Organisation criteria) after the first week of treatment. This neutropenia disappeared after another week, and the counts were normal from then on. All other patients had normal white blood cell counts. The assessment of toxicity was according to the WHO criteria: grade 0 (non-toxic, a count of more than 4×10^9 leukocytes per liter), grade 1 (mild) to grade 4 (most severe). No cases of vomiting, nausea, or diarrhoea were recorded.

The most up to date information is that most of the patients are still in remission one month after the last injection. Three patients were not cleared entirely, but the disease is in such mild manifestation that it can be well treated with conventional

remedies, such as ointments. All these patients previously suffered greatly from their psoriasis which was refractory to other treatments.

5 In a separate study, which has been in progress for a longer period, of three patients with refractory psoriasis, one patient is still relatively free of lesions and symptoms after one year. This patient, who previously suffered distressing refractory psoriasis, can be treated with conventional emollients. Dexrazoxane therefore has the potential to provide remarkable long term relief from refractory psoriasis and a low level of side effects.

10

EXAMPLE 5

A solution for infusion is prepared:

15

Cardioxane[®] is available in 36ml brown glass vials. Each vial contains 500mg lyophilised active substance, the hydrochloric acid salt of dexrazoxane. For reconstitution the contents of each vial is dissolved in 25ml sterile water for injection. The contents will dissolve within a few minutes under gentle agitation. The pH of the resulting solution is approx. pH 1.6.

20

For infusion the solution needs to be further diluted. Preferred are sodium lactate UP (0.16M) or Ringer-Lactate BP for infusion. Both solutions give an infusion fluid with an acceptable pH.

25

Dilution of 4 vials of Cardioxane [®] (reconstituted)			
Solution	Volume (ml)	pH	Total volume after dilution (ml)
Sodium lactate UP	500	4.66	600

(0.16M)	300	4.47	400
	100	3.80	200
Ringer-Lactate BP	500	3.45	600
	400	3.19	500
	300	2.85	400
	100	2.14	200

EXAMPLE 6:

- 5 Tablets of the following composition are prepared:

	mg / tablet
Cardioxane [®]	100 mg
Avicel [®] (microcrystalline cellulose)	16 mg
10 starch	9 mg
hydroxypropylmethyl cellulose	3 mg
magnesium stearate	1 mg
polyvinylpyrrolidone	0.6 mg
colloidal silicon dioxide	0.3 mg

15

Half the total quantity of hydroxypropylmethyl cellulose, polyvinylpyrrolidone and a sufficient amount of water are mixed together and stirred until dissolved (binder solution). Cardioxane[®], starch, and the rest of the hydroxypropylmethyl cellulose are mixed in a granulator and stirred for 10 minutes. The granulation process is started
 20 by spraying the binder solution. After spraying and blending the product is dried in the same apparatus and discharged when the water content is below 2.8-3.0%. The granulate is passed through an oscillating granulator equipped with a 1.2mm stainless steel screen. The granulate is mixed with starch, microcrystalline cellulose, and colloidal silicon dioxide for 20 minutes under rotation. The magnesium stearate is

added and blended with the granulate. The final product is compressed at 130 mg on a rotary tableting unit equipped with 10 mm diameter lenticular punches.

5 EXAMPLE7:

An ointment of the following composition is prepared:

	g / 100 g ointment
10 Cardioxane [®]	1.5 g
liquid paraffin	10 g
polyoxyethylene-20-stearylether	15 g
propyleneglycol	5 g
white vaseline	40 g
15 purified water	28.5 g

Cardioxane[®] is reconstituted in cold water. The other ingredients are melted at 60°C and stirred. Cardioxane[®] is added and the product is stirred until cold.

20

EXAMPLE8:

A cream of the following composition is prepared:

	g / 100 g cream
25 Cardioxane [®]	1 g
glycerinmonostearate (Tegin M [®])	4 g
PEG-20-glycerinmonostearate (Tagat S2 [®])	7 g
cetylstearyl-alcohol	6 g
30 viscous paraffin	7.5 g
white vaseline	25 g

glycerol 85%	10 g
magnesium sulfate heptahydrate	0.5 g
purified water	39 g

- 5 The glycerinemonostearate, PEG-20-glycerinemonostearate, cetylstearyl-alcohol, paraffin and vaseline are heated to 60°C and stirred. The smaller part of the water is briefly boiled and cooled to 60°C, the magnesium sulfate and glycerol are added and stirred. Cardioxane[®] is reconstituted in the other part of the water and added to the solution. Now the two phases are emulsified in an emulsifier, and after cooling a
10 homogeneous creme is obtained.

EXAMPLE 9:

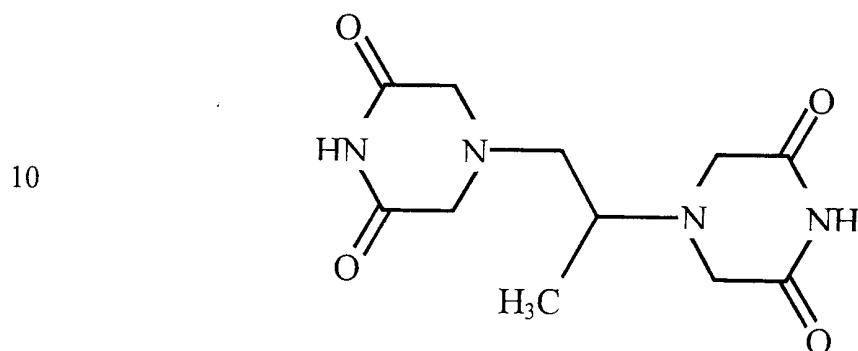
- 15 A gel of the following composition is prepared:

	g / 100 g gel
Cardioxane [®]	1.2 g
isopropyl alcohol	20 g
glycerol 100 %	2 g
20 hydroxyethyl cellulose	1.8 g
purified water	75 g

- Half of the total quantity of water, and glycerol are heated to 50°C; hydroxyethyl cellulose is added and stirred until a homogeneous gel is obtained. Cardioxane[®] is
25 reconstituted with the rest of the water and added under constant stirring. The gel is cooled to 25°C, the isopropyl alcohol is added and the mixture is stirred under vacuum until a homogeneous gel is obtained.

CLAIMS:

1. The use for the manufacture of a medicament for treating psoriasis of
dexrazoxane, the d-isomer of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane, a compound
5 of formula



or a physiologically acceptable salt thereof.

- 15
2. The use of claim 1 wherein the physiologically acceptable salt is
dexrazoxane.HCl.
3. The use of claim 1 or claim 2 wherein the medicament is for injection or
20 infusion.
4. The use of claim 3 wherein the medicament comprises powder for
reconstitution into solution prior to injection.
- 25 5. The use of claim 1 or claim 2 wherein the medicament is in topically,
transdermally or percutaneously administered form.
6. The use of claim 5 wherein the medicament is in the form of an ointment,
lotion or plaster.
- 30 7. The use of claim 1 or claim 2 wherein the medicament is in peroral form.

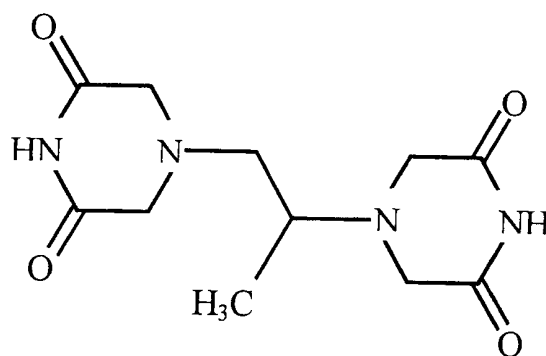
8. The use of claim 1 or claim 2 wherein the medicament is in the form of a suppository.
- 5 9. The use of claim 3 or claim 4 wherein the medicament is in unit dosage form and comprises about between about 250 mg and about 750 mg (e.g. 500mg) dexrazoxane, calculated as dexrazoxane hydrochloride.
- 10 10. The use of claim 3 or claim 4 wherein the medicament is in unit dosage form and comprises between about 750 mg and about 1250 mg (e.g. about 1000mg) dexrazoxane calculated as dexrazoxane hydrochloride.
- 15 11. The use of claim 3 or claim 4 wherein the medicament is in unit dosage form and comprises between about 1250 mg and about 1750 mg (e.g. about 1500mg) dexrazoxane calculated as dexrazoxane hydrochloride.
- 20 12. The use of claim 11 wherein the medicament is in the form of a topical formulation in which the dexrazoxane in the medicament is at a concentration of from about 0.1 wt % to about 5 wt %, calculated as dexrazoxane hydrochloride.
13. The use of claim 11 wherein the medicament is adapted for topical administration to the exclusion of oral or parenteral administration or administration by injection or infusion.
- 25 14. The use of claim 1 or claim 2 wherein the medicament is an injectable or infusible formulation and is for administration to an adult by a protocol comprising:
- (a) administering the medicament by infusion or injection in a dosage of between about 250 mg and 750 mg calculated as dexrazoxane hydrochloride;

(b) on a subsequent day administering the medicament by infusion or injection in a dosage of between about 750 mg and 1250 mg calculated as dexrazoxane hydrochloride;

(c) on a subsequent day administering the medicament by infusion or injection in a dosage of between about 1250 mg and about 1750 mg calculated as dexrazoxane hydrochloride.

15. A product, especially comprising a topical or parenteral formulation, containing dexrazoxane or a physiologically acceptable salt thereof and an agent useful for treating psoriasis or relieving its symptoms as a combined preparation for simultaneous, separate or sequential use in treating psoriasis.

16. A method of treating psoriasis in a patient, comprising administering to the patient a therapeutically effective amount of dexrazoxane, the d-isomer of 1,2-bis(3,5-dioxopiperazin-1-yl)-propane, a compound of formula



or a physiologically acceptable salt thereof.

17. The method according to claim 16 wherein the dexrazoxane is administered together with a physiologically acceptable diluent, carrier or excipient.

18. The method according to claim 16 or claim 17 wherein the physiologically acceptable salt is dexrazoxane.HCl.

19. The method according to any of claims 16 to 18 wherein the dexrazoxane is administered by injection or infusion.

5 20. The method according to any of claims 16 to 18 wherein the dexrazoxane is administered topically, transdermally or percutaneously.

21. The method according to claim 20 wherein the dexrazoxane is in the form of an ointment, lotion or plaster.

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22. The method according to any of claims 16 to 18 wherein the dexrazoxane is administered orally.

15 23. The method according to any of claims 16 to 18 wherein the dexrazoxane is in the form of a suppository.

24. The method according to any of claims 16 to 23 wherein the patient is an adult and the method comprises the step of administering the dexrazoxane by infusion or injection in a dosage of between about 250mg and about 750mg
20 calculated as dexrazoxane hydrochloride.

25. The method according to any of claims 16 to 24 wherein the patient is an adult and the method comprises the step of administering the dexrazoxane by infusion or injection in a dosage of between about 750mg and about 1250mg
25 calculated as dexrazoxane hydrochloride.

26. The method according to any of claims 16 to 25 wherein the patient is an adult and the method comprises the step of administering the dexrazoxane by infusion or injection in a dosage of between about 1250mg and about 1750mg
30 calculated as dexrazoxane hydrochloride.

27. The method according to any of claims 16 to 23 wherein the patient is an adult and the method comprises the steps of

5 (a) administering the dexrazoxane by infusion or injection in a dosage of between about 250mg and about 750mg calculated as dexrazoxane hydrochloride;

(b) on a subsequent day administering the dexrazoxane by infusion or injection in a dosage between about 750mg and about 1250mg calculated as dexrazoxane hydrochloride; and

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(c) on a subsequent day administering the dexrazoxane by infusion or injection in a dosage between about 1250mg and about 1750mg calculated as dexrazoxane hydrochloride.

15 28. The method according to claim 16 wherein the dexrazoxane is administered topically.

29. The method according to claim 28 wherein the dexrazoxane is administered as a topical formulation containing from about 1 wt % to about 2 wt % dexrazoxane
20 calculated as dexrazoxane hydrochloride.

29. A method for the manufacture of a medicament for treating psoriasis, comprising formulating dexrazoxane or a physiologically acceptable salt thereof into such a medicament.

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30. A method of claim 30 which further includes the feature(s) of any one or more of claims 2 to 14.

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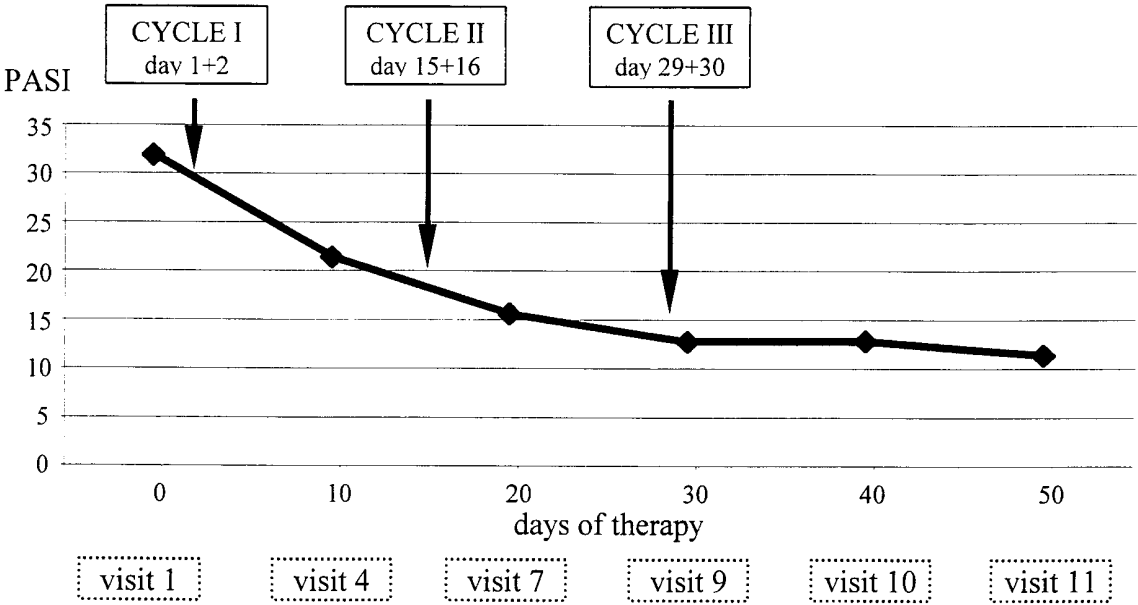


FIGURE 1