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(54) Benevnelse **Paracetamol for parenteral administration**

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The invention relates to pharmaceutical formulations of the active ingredient paracetamol (acetaminophen), which are suitable for parenteral administration, in particular infusion.

Paracetamol is a very widely employed active ingredient having excellent tolerability (cf., for example, G. G. Graham et al., Drug Safety, 2005, 28(3), 227-40). Paracetamol is commercially obtainable in numerous pharmaceutical forms, in particular as an oral administration form. In certain cases, for example in the course of intensive care or if oral administration is not possible for certain reasons, parenteral administration of paracetamol is desirable.

The pharmacopeia understands parenterals as meaning sterile preparations that are intended for injection, infusion or implantation. Parenterals must in principle be prepared with particular care in order to guarantee non-irritancy and to avoid microbial and particulate contamination. Excipients are especially substances for improving solubility, substances for isotonicization, buffers, antioxidants, chelating agents, preservatives, emulsifiers and excipients for prolonging action.

Aqueous parenterals must be iso-osmotic or approximately iso-osmotic to the plasma or lymph. In the case of severe hypo- or hyperosmotic differences, erythrocyte damage or tissue irritation usually occurs. In the case of intravenous administration of strong hypo-osmotic solutions hemolysis occurs, in the case of supply of relatively large amounts of hyperosmotic solutions plasmolysis occurs.

The pH of aqueous parenterals also plays an important role. Blood serum is provided with the four buffer systems carbonic acid/hydrogencarbonate, plasma

proteins, primary/secondary phosphate and hemoglobin/oxyhemoglobin. The pH of the blood is between 7.30 and 7.45. An approximation of the pH of infusion solutions to the physiological pH range (isohydria) is often not possible for stability reasons. Only a best-possible approximation to the physiological pH range (euhydria) is then carried out. The tolerance range for infusion solutions is in general between pH 3.0 and 10.5. Depending on the difference of the actual pH from the physiological pH range, a sufficiently slow infusion is then necessary to make possible an approximation of the physiological pH range to the buffer systems of the blood.

Buffering of infusion solutions, e.g. with acetate, phosphate or citrate buffers, has the disadvantage that the natural pH stabilization of the blood is superposed. In order to retain the natural pH stabilization of the blood, buffering of infusion medicaments should therefore not take place if possible. The adjustment of the pH with strong acids or bases (e.g. HCl or NaOH), on the other hand, does not result in any buffer action and is therefore less questionable.

Infusion solutions of paracetamol are known in the prior art.

In the Federal Republic of Germany, an infusion solution of paracetamol is marketed under the name Perfalgan®. The infusion solution is indicated for short-term treatment of moderately severe pain, particularly after operations, and for the short-term treatment of fever if intravenous administration is clinically justified because of urgently necessary pain or fever treatment or if other types of administration are not possible. The administration takes place as a 15-minute infusion. In addition to paracetamol, the

infusion solution contains as other constituents cysteine hydrochloride monohydrate, sodium monohydrogenphosphate dihydrate, hydrochloric acid, mannitol, sodium hydroxide and water for injection. The content of sodium is stated as 0.04 mg/ml. The shelflife is stated as 2 years, where storage should not take place above 30°C or in a refrigerator.

EP-A 916 347 discloses buffered paracetamol injection forms based on organic solvents, in particular ethanol and benzyl alcohol. Chelating agents and antioxidants are added as stabilizers.

US-A 2005/0203175 discloses buffered compositions for parenteral administration of paracetamol in combination with lidocaine HCl, which contain, inter alia, organic solvents, chelating agents and antioxidants.

WO 02/072080 relates to buffered aqueous solutions of paracetamol and antioxidants selected from the group consisting of ascorbic acid, N-acetyl-l-cysteine and other SH group-containing stabilizers. The solutions are rendered isotonic using NaCl.

US 6,028,222 discloses buffered aqueous solutions of paracetamol which contain a free radical scavenger or free radical antagonists.

WO 03/033026 relates to aqueous solutions of pracetamol which contain propylene glycol and citrate buffer and are obtainable by means of a designated heat treatment.

EP-A 1 889 607 discloses buffered aqueous solutions of paracetamol, which contain glucose, fructose or gluconate and formaldehyde sulfoxylate, sodium sulfite or sodium dithionite.

EP-A 1 752 139 relates to aqueous solutions of paracetamol and antioxidants selected from the group consisting of ascorbic acid, N-acetyl-l-cysteine and other SH group-containing stabilizers. The solutions are rendered isotonic using NaCl and have an oxygen content of less than 1 mg/l.

US 6,992,218 and FR-A 2 809 619 relate to processes for the preparation of buffered, aqueous solutions of paracetamol having an oxygen content of less than 2 ppm.

US 2006/0084703 discloses aqueous formulations of paracetamol, which contain buffer, isotonicizing agent and a paracetamol dimer.

US 2006/0292214 relates to compositions which contain paracetamol in nanoparticulate form.

The pharmaceutical compositions known from the prior art for the parenteral administration of paracetamol, however, are not satisfactory in every respect. Paracetamol is comparatively poorly soluble and sensitive to oxidation, which is why appropriate measures are customarily taken in order to guarantee an adequate storage stability of the compositions.

Thus the pharmaceutical compositions for parenteral administration of paracetamol are customarily buffered, such that the natural buffer action of the blood is superposed by the buffers and, where appropriate, an only comparatively slow infusion is possible. In the case of phosphate buffers, in particular with divalent metal cations ($Ca^{2+}$, $Mg^{2+}$), insoluble complexes can be formed. This can have an adverse effect, not only in patients with appropriate deficiency symptoms, but also complicates co-infusion with appropriate electrolyte

solutions, which can be indicated under certain circumstances.

Furthermore, many of the known pharmaceutical compositions contain comparatively high electrolyte concentrations, in particular also sodium ions, which can lead to an osmotic shift of water from the cells into the interstitium.

Moreover, the pharmaceutical compositions for the parenteral administration of paracetamol customarily contain a multiplicity of different ingredients, which is disadvantageous, inter alia, from the economic point of view. Because of the particular requirements of parenterals, particular purity criteria must be maintained and regularly monitored analytically. Thus the known pharmaceutical compositions for the parenteral administration of paracetamol customarily contain certain antioxidants, which can cause incompatibilities and side effects. If such antioxidants are dispensed with, this customarily results in a lower storage stability.

The invention is based on the object of making available pharmaceutical compositions for parenteral administration, which have advantages compared to the compositions of the prior art.

This object is achieved by the subject matter of the patent claims.

It has surprisingly been found that paracetamol can be stabilized against oxidative degradation if the electrolyte concentration is kept low. The addition of electrolytes leads to destabilization.

If the electrical conductivity is taken as a measure of the content of electrolytes, the storage stability decreases with increasing electrical conductivity. It

is possible by this means to prepare compositions for parenteral administration of paracetamol, in particular infusion solutions, which manage with a minimum of ingredients and nevertheless have an adequate storage stability.

If consistently nonionic or zwitterionic compounds, which outwardly are electrically neutral, are added as ingredients, these virtually do not increase the electrical conductivity of the composition, by means of which the high storage stability of the composition is retained and, if required, depending on the type of ingredient, can be further improved.

The invention relates to an aqueous pharmaceutical composition for parenteral administration, which contains paracetamol and has an electrical conductivity of at most 200 µS $cm^{-1}$, wherein the composition contains no C1-C6 alkanols and no polyethylenglykol.

The composition according to the invention is aqueous. Since it is intended for parenteral administration, it preferably contains water for injection (Ph. Eur.). Preferably, water for injection is the only liquid constituent of the composition according to the invention. Thus the composition according to the invention preferably contains no organic solvents. Among these come all essentially low molecular weight organic compounds known to the person skilled in the art, which are employed exclusively for the purpose of increasing the solubility of paracetamol in water. These especially include alcohols such as ethanol, benzyl alcohol and other low molecular weight organic compounds that contain hydroxyl groups.

Preferentially, in the composition according to the invention, all ingredients are present in completely dissolved form, i.e. it is preferably not a dispersion,

neither an emulsion nor a suspension. The composition according to the invention is preferably particle- and discoloration-free.

The composition according to the invention contains paracetamol (acetaminophen). The paracetamol is preferably present in completely dissolved form. The concentration of the paracetamol in the composition according to the invention is preferably below its saturation concentration, particularly preferably at least 95% below its saturation concentration at room temperature. In a preferred embodiment, the concentration of the paracetamol is in the range from 10.0 ± 7.5 g $l^{-1}$,10.0 ± 6.0 g $l^{-1}$,10.0 ± 5.0 g $l^{-1}$,10.0 ± 4.0 g $l^{-1}$,10.0 ± 3.0 g $l^{-1}$ or 10.0 ± 2.5 g $l^{-1}$; more preferably 10.0 ± 2.0 g $l^{-1}$, even more preferably 10.0 ± 1.5 g $l^{-1}$, most preferably 10.0 ± 1.0 g $l^{-1}$, and in particular 10.0 ± 0.5 g $l^{-1}$, based on the composition.

In a preferred embodiment, the content of paracetamol is either less than 1.2% by weight or more than 1.3% by weight, based on the composition.

The composition according to the invention can contain further active ingredients in addition to paracetamol. Preferably, the composition according to the invention, however, contains paracetamol as the only active ingredient.

The composition according to the invention has an electrical conductivity of at most 200 µS $cm^{-1}$. The measurement of the electrical conductivity of aqueous solutions is known to the person skilled in the art and suitable measuring apparatuses are obtainable commercially. The electrical conductivity is preferably measured at room temperature. Preferably, the electrical conductivity of the composition according to the invention is at most 190 µS $cm^{-1}$, at most 180 µS $cm^{-}$

$^{-1}$, at most 170 µS cm$^{-1}$, at most 160 µS cm$^{-1}$, at most 150 µS cm$^{-1}$, at most 140 µS cm$^{-1}$, at most 130 µS cm$^{-1}$, at most 120 µS cm$^{-1}$ or at most 110 µS cm$^{-1}$; more preferably at most 100 µS cm$^{-1}$, at most 90 µS cm$^{-1}$, at most 80 µS cm$^{-1}$, at most 70 µS cm$^{-1}$, or at most 60 µS cm$^{-1}$; even more preferably at most 50 µS cm$^{-1}$, at most 40 µS cm$^{-1}$, or at most 30 µS cm$^{-1}$; most preferably at most 25 µS cm$^{-1}$, at most 20 µS cm$^{-1}$ or at most 15 µS cm$^{-1}$; and in particular at most 12.5 µS cm$^{-1}$, at most 10 µS cm$^{-1}$ or at most 7.5 µS cm$^{-1}$.

The composition according to the invention is therefore distinguished by a comparatively low electrical conductivity. Thus in comparison the electrical conductivity of an isotonic saline solution (0.9% by weight of NaCl) is more than 7500 µS cm$^{-1}$. The electrical conductivity of aqueous compositions is essentially influenced by ions. It can be predicted on the basis of the square root law according to Kohlrausch or the Debye-Hückel-Onsager theory. As illustrated in more detail in the experimental section, paracetamol itself virtually does not contribute to the electrical conductivity (10 g of paracetamol in 1000 ml of water: about 4 µS/cm). An addition of 100 mg of NaCl to this active ingredient solution (0.01% by weight of NaCl), however, already leads to an increase in the electrical conductivity to about 200 µS/cm.

In connection with pharmaceutical compositions for parenteral administration, electrolytes and buffers in particular have an influence on the electrical conductivity. Accordingly, the composition according to the invention contains, if at all, at most a comparatively small amount of electrolytes and/or buffer substances.

In a preferred embodiment, the composition according to the invention contains virtually no trivalent

electrolytes, e.g. $PO_4^{3-}$ and $HOC(CO_2^-)_3$. In another preferred embodiment, the composition according to the invention contains virtually no divalent electrolytes, e.g. $Ca^{2+}$, $Mg^{2+}$, $HPO_4^{2-}$ and $HOC(CO_2^-)_2CO_2H$. In a further preferred embodiment, the composition according to the invention contains virtually no monovalent electrolytes, e.g. $Na^+$, $K^+$, $NH_4^+$, $Cl^-$, $CH_3CO_2^-$, $H_2PO_4^-$ and $HOCCO_2^-(CO_2H)_2$.

In a preferred embodiment, the composition according to the invention has a buffer capacity β of at most 5 mmol $l^{-1}$ $pH^{-1}$. The definition and the determination of the buffer capacity β are known to the person skilled in the art. In general, the buffer capacity is that amount of substance of a strong proteolyte (acid or base), which is necessary in order to change the pH of the composition by one unit. Preferably, the measurement of the buffer capacity takes place at room temperature.

Preferably, the composition according to the invention has a buffer capacity β of at most 4.5 mmol $l^{-1}$ $pH^{-1}$, at most 4.0 mmol $l^{-1}$ $pH^{-1}$, at most 3.5 mmol $l^{-1}$ $pH^{-1}$, at most 3.0 mmol $l^{-1}$ $pH^{-1}$, at most 2.5 mmol $l^{-1}$ $pH^{-1}$, at most 2.0 mmol $l^{-1}$ $pH^{-1}$, at most 1.5 mmol $l^{-1}$ $pH^{-1}$, or at most 1.0 mmol $l^{-1}$ $pH^{-1}$; preferably at most 0.9 mmol $l^{-1}$ $pH^{-1}$, at most 0.8 mmol $l^{-1}$ $pH^{-1}$, at most 0.7 mmol $l^{-1}$ $pH^{-1}$, at most 0.6 mmol $l^{-1}$ $pH^{-1}$, at most 0.5 mmol $l^{-1}$ $pH^{-1}$, at most 0.4 mmol $l^{-1}$ $pH^{-1}$, at most 0.3 mmol $l^{-1}$ $pH^{-1}$, at most 0.2 mmol $l^{-1}$ $pH^{-1}$, or at most 0.1 mmol $l^{-1}$ $pH^{-1}$; even more preferably at most 0.09 mmol $l^{-1}$ $pH^{-1}$, at most 0.08 mmol $l^{-1}$ $pH^{-1}$, at most 0.07 mmol $l^{-1}$ $pH^{-1}$, at most 0.06 mmol $l^{-1}$ $pH^{-1}$, at most 0.05 mmol $l^{-1}$ $pH^{-1}$, at most 0.04 mmol $l^{-1}$ $pH^{-1}$, at most 0.03 mmol $l^{-1}$ $pH^{-1}$, at most 0.02 mmol $l^{-1}$ $pH^{-1}$ or at most 0.01 mmol $l^{-1}$ $pH^{-1}$; most preferably at most 0.009 mmol $l^{-1}$ $pH^{-1}$, at most 0.008 mmol $l^{-1}$ $pH^{-1}$, at most 0.007 mmol $l^{-1}$ $pH^{-1}$, at most 0.006 mmol $l^{-1}$ $pH^{-1}$, or at most 0.005 mmol $l^{-1}$ $pH^{-1}$; particularly preferably the

composition according to the invention is virtually unbuffered.

Preferably, the composition according to the invention has a pH in the range from 5.0 to 7.5. In a preferred embodiment, the composition according to the invention has a pH in the range from 5.5 ± 0.5, more preferably 5.5 ± 0.4, even more preferably 5.5 ± 0.3, most preferably 5.5 ± 0.2 and in particular 5.5 ± 0.1. In another preferred embodiment, the composition according to the invention has a pH in the range from 6.0 ± 0.5, more preferably 6.0 ± 0.4, even more preferably 6.0 ± 0.3, most preferably 6.0 ± 0.2 and in particular 6.0 ± 0.1. In a further preferred embodiment, the composition according to the invention has a pH in the range from 6.5 ± 0.5, more preferably 6.5 ± 0.4, even more preferably 6.5 ± 0.3, most preferably 6.5 ± 0.2 and in particular 6.5 ± 0.1. In another preferred embodiment, the composition according to the invention has a pH in the range from 7.0 ± 0.5, more preferably 7.0 ± 0.4, even more preferably 7.0 ± 0.3, most preferably 7.0 ± 0.2 and in particular 7.0 ± 0.1.

In a particularly preferred embodiment, the pH of the composition according to the invention is native, i.e. it is fixed by the ingredients and influenced neither by the addition of buffer nor by the addition of strong acid or base.

Preferably, the composition according to the invention contains one or more nonionic isotonicizing agents. Suitable nonionic isotonicizing agents are known to the person skilled in the art, in particular glucose, fructose and mannitol. Preferably, the nonionic isotonicizing agent is a sugar alcohol, in particular mannitol (mannite).

The concentration of the nonionic isotonicizing agent, preferably mannitol, is preferably in the range from 35 ± 25 $gl^{-1}$, more preferably 35 ± 20 $gl^{-1}$, even more preferably 35 ± 15 $gl^{-1}$, most preferably 35 ± 10 $gl^{-1}$, and in particular 35 ± 5 $gl^{-1}$, based on the composition. In a preferred embodiment, the absolute content of mannitol is either less than 0.91% by weight or more than 1.17% by weight, based on the composition.

Preferably, the proportion by weight of the nonionic isotonicizing agent, preferably mannitol, is greater than the proportion by weight of paracetamol in the composition according to the invention. Preferably, the relative weight ratio of nonionic isotonicizing agent:paracetamol is > 1:1, more preferably > 1.5:1, even more preferably > 2:1, most preferably > 2.5:1 and in particular > 3:1 or > 3.5:1. In a preferred embodiment, the relative weight ratio of paracetamol to mannitol is either greater than 1:0.7 or less than 1:1.

In a preferred embodiment, the composition according to the invention contains cysteine, if appropriate additionally to mannitol. Although cysteine is present at pH 7 as a zwitterion, it is interpreted according to the invention because of its electroneutrality as a nonionic isotonicizing agent, which virtually does not contribute to the electrical conductivity of the composition. It was found that cysteine at pH 5.5 to 7 has no buffer properties at all.

The concentration of the cysteine is preferably in the range from 0.1 ± 0.09 $gl^{-1}$, more preferably 0.1 ± 0.08 $gl^{-1}$, even more preferably 0.1 ± 0.07 $gl^{-1}$, most preferably 0.1 ± 0.06 $gl^{-1}$, and in particular 0.1 ± 0.05 $gl^{-1}$, based on the composition.

Preferably, the proportion by weight of paracetamol is greater than the proportion by weight of cysteine in

the composition according to the invention. Preferably, the relative weight ratio of paracetamol:cysteine is > 50:1, more preferably > 60:1, even more preferably > 70:1, most preferably > 80:1 and in particular > 90:1 or > 95:1.

In a preferred embodiment, the composition according to the invention contains both mannitol and cysteine. In this case, the proportion by weight of mannitol is preferably greater than the proportion by weight of cysteine in the composition according to the invention. Preferably, the relative weight ratio of mannitol:cysteine is > 100:1, more preferably > 200:1, even more preferably > 250:1, most preferably > 300:1 and in particular > 350:1 or > 360:1.

In a preferred embodiment, the composition according to the invention contains, if at all, altogether at most 100 mmol/l of alkali metal cations, more preferably altogether at most 10 mmol/l, even more preferably altogether at most 1.0 mmol/l, most preferably altogether at most 0.1 mmol and in particular altogether at most 0.01 mmol/l. In a preferred embodiment, the composition according to the invention contains virtually no salt, neither dissolved nor solid. In this composition, zwitterionic compounds under isoelectric conditions, e.g. amino acids such as cysteine, are not interpreted as salts.

In a preferred embodiment, the composition according to the invention contains no chelating agents, e.g. EDTA.

In a preferred embodiment, the composition according to the invention contains altogether at most 5 ingredients, i.e. in addition to paracetamol and water the composition consists of at most 3 further ingredients. Ionic compounds which dissociate in water to give cations and anions count here as 2 compounds.

Particularly preferably, the composition according to the invention contains at most 4 ingredients. Particularly preferably, the composition according to the invention consists of water, paracetamol and mannitol and/or cysteine.

In a particularly preferred embodiment, the composition according to the invention contains, in addition to water, paracetamol and one or more non-ionic isotonicizing agents, no further ingredients at all.

The composition according to the invention is intended for parenteral administration, in particular for intravenous infusion. For this purpose, it is necessary for the composition to have a physiologically tolerable osmolarity (or osmolality). Preferably, the composition according to the invention has an osmolarity of at least 0.22 osmol $l^{-1}$, more preferably at least 0.23 osmol $l^{-1}$, more preferably at least 0.24 osmol $l^{-1}$, even more preferably at least 0.25 osmol $l^{-1}$, most preferably at least 0.26 osmol $l^{-1}$, and in particular at least 0.27 osmol $l^{-1}$. Preferably, the composition according to the invention has an osmolarity of at most 0.36 osmol $l^{-1}$, more preferably at most 0.34 osmol $l^{-1}$, more preferably at most 0.32 osmol $l^{-1}$, even more preferably at most 0.30 osmol $l^{-1}$, most preferably at most 0.29 osmol $l^{-1}$,and in particular at most 0.28 osmol $l^{-1}$. In comparison, an isotonic saline solution contains 0.9% (mass percent) of sodium chloride and corresponds with an osmolarity of 308 mosmol/l approximate to that of blood plasma. The theoretical osmolarity of a Ringer infusion solution is 309 mOsm/l. The theoretical osmolarity of a Ringer lactate solution is between 262 and 293 mOsm/l.

The composition according to the invention is distinguished by an outstanding storage stability. It has surprisingly been found that with low electrical

conductivity, and accompanying it, correspondingly lower electrolyte concentration, buffer substances can be completely dispensed with and an adequate storage stability is nevertheless achieved. Preferably, the content of paracetamol after storage at 60°C for 4 weeks in closed vessels is at least 99.0% of the paracetamol originally contained in the composition, i.e. before storage, more preferably at least 99.2%, even more preferably at least 99.4%, most preferably at least 99.6% and in particular at least 99.8%, preferably under the conditions illustrated more closely in the experimental section.

The composition according to the invention can be prepared by conventional processes known to the person skilled in the art. Preferably, firstly here

A) water for injection with an oxygen content of less than 0.50 mg/l is introduced;

B) paracetamol and the further ingredients are dissolved in the water A) in the desired amounts with as extensive exclusion of oxygen as possible; and

C) if required the pH of the solution is adjusted to the desired value by addition of a physiologically tolerable acid or base.

Expediently

D) the solution adjusted to the desired pH is then filtered through a 0.2 µm membrane filter, subsequently filled into containers for infusion solutions and heat-sterilized at 121°C for 15 min.

A further preferred variant of the process for the preparation of the solution according to the invention provides for an inert gas to be led through the water in step A) for driving out the oxygen and that during mixing in step B) and if appropriate in all further steps for work to be carried out under an inert gas atmosphere.

A further aspect of the invention relates to containers which contain the composition according to the invention. Here, the composition according to the invention is preferably present as a "Ready-to-use" preparation, i.e. can be used immediately. In particular, preferably no dilution or dissolution steps are necessary before use.

The composition according to the invention is preferably packaged in containers customary for parenteral preparations. The containers can be bottles or bags, such as are customary for injection-ready solutions. Containers made of glass or plastic are preferred. If they are plastic containers, these preferably consist of a material based on polyolefins and are optionally surrounded by a second bag, which contains an oxygen barrier layer, possibly with an oxygen absorber between the bags. Suitable packaging materials are known to the person skilled in the art. In this connection, reference can be made fully, for example, to E. Bauer, Pharmaceutical Packaging Handbook, Informa Health Care 2009; or D. A. Dean, Pharmaceutical Packaging Technology, Taylor & Francis 2000.

The composition according to the invention can be packaged under protective gas, for example under $N_2$, $CO_2$ or Ar. In a preferred embodiment, the composition according to the invention has a content of dissolved oxygen of at most 50 ppm, more preferably at most 20 ppm, even more preferably at most 10 ppm, most preferably at most 5 ppm and in particular at most 2 ppm or at most 1 ppm.

Preferably, the composition is free of organic solvents, has a pH in the range from 5.5 to 7 and an oxygen content of at most 2.00 mg/l, more preferably at

most 1.50 mg/l, even more preferably at most 1.25 mg/l, most preferably at most 1.00 mg/l and in particular at most 0.50 mg/l.

The parenteral administration of the composition according to the invention can basically be carried out in all customary ways, in particular intravenously, intra-arterially, subcutaneously, intramuscularly, intraventricularly, intracapsularly, intraocularly, intraspinally, intracisternally, intraperitoneally, intranasally or as an aerosol. Preferably, administration is carried out intravenously, wherein the composition is preferably present as an infusion solution.

In a preferred embodiment, the composition according to the invention is an infusion solution which is prepared for intravenous infusion over a period of time of 2 minutes to 24 hours, more preferably over a period of time of 3 minutes to 6 hours, even more preferably 5 minutes to 1 hour, most preferably 10 minutes to 45 minutes and in particular 15 minutes.

A further aspect of the invention relates to the composition described above for the treatment of pain or the use of paracetamol for the production of a composition described above for the treatment of pain. Preferably the pain is moderately strong pain, preferably post-operative pain.

In a preferred embodiment, the patient is a geriatric or paediatric patient.

The following examples serve to illustrate the invention, but are not designed to be restrictive:

Aqueous solutions of paracetamol and further ingredients were prepared. The electrical conductivity

of the solutions was measured and the storage stability of paracetamol was determined by means of the formation of degradation products (for the formation of the dimer cf., for example, D. W. Pottert et al, J Biol Chem, 1985, 280(22), 12174-80; W. Clegg et al., Acta Crystallographica, 1998, C54, 1881-2).

The results are summarized in the following two tables:

| Ex. | in 500 ml of $H_2O$ for injection | | | electrical conductivity [µS $cm^{-1}$] | dimer [% rel. to paracetamol] | | | | impurities overall [% rel. to paracetamol] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | paracetamol [g] | mannitol [g] | NaCl [mg] | | autoclaved | 1 week 60°C | 2 weeks 60°C | 4 weeks 60°C | autoclaved | 1 week 60°C | 2 weeks 60°C | 4 weeks 60°C |
| 1 | 5.0 | - | - | 3.15 | 0.018 | 0.053 | 0.083 | 0.104 | 0.050 | 0.097 | 0.141 | 0.177 |
| 2 | 5.0 | 18.35 | - | 3.24 | 0.012 | 0.030 | 0.045 | 0.060 | 0.041 | 0.072 | 0.095 | 0.128 |
| 3 | 5.0 | - | 1.0 | 5.22 | 0.037 | 0.094 | 0.093 | 0.112 | 0.079 | 0.161 | 0.161 | 0.191 |
| 4 | 5.0 | - | 2.5 | 11.45 | 0.028 | 0.062 | 0.101 | 0.142 | 0.067 | 0.111 | 0.170 | 0.228 |
| 5 | 5.0 | - | 12.2 | 49.6 | 0.021 | 0.077 | 0.101 | 0.128 | 0.056 | 0.130 | 0.172 | 0.213 |
| 6 | 5.0 | - | 25.1 | 99.2 | 0.048 | 0.151 | 0.145 | 0.230 | 0.101 | 0.232 | 0.223 | 0.337 |
| 7 | 5.0 | - | 48.7 | 199.9 | 0.039 | 0.088 | 0.111 | 0.146 | 0.085 | 0.155 | 0.185 | 0.237 |

| Ex. | to 1000 ml of $H_2O$ for injection | | | pH | electrical conductivity [µS $cm^{-1}$] | dimer [% rel. to paracetamol] | | |
|---|---|---|---|---|---|---|---|---|
| | paracetamol [g] | mannitol [g] | NaCl [g] | | | start | 3 months 40°C | 6 months 40°C |
| 8 | 10.0 | 36.70 | - | 5.5(native) | 11.15 | 0.0000 | 0.0126 | 0.0191 |
| 9 | 10.0 | - | 9.0 | 6.2 (NaOH) | 10430.00 | 0.0110 | 0.1881 | 0.3317 |



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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10 | 10.0 | 36.70 | - | 7.0 (NaOH) | 38.20 | 0.0053 | 0.0185 | 0.0218 |
| 11 | - | - | isotonic | native | 7660 | - | - | - |

**P a t e n t k r a v**

**1.** Vandig farmasøytisk sammensetning i form av en infusjonsløsning, som inneholder paracetamol og har en elektrisk ledningsevne på høyst 100 µS $cm^{-1}$, hvorved sammensetningen ikke inneholder noen organiske løsemidler.

**2.** Sammensetning ifølge krav 1, karakterisert ved at den har en elektrisk ledningsevne på høyst 50 µS $cm^{-1}$.

**3.** Sammensetning ifølge krav 1 eller 2, karakterisert ved at den har en bufferkapasitet β på høyst 5,0 mmol $l^{-1}$ $pH^{-1}$.

**4.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den har en pH-verdi i området fra 5,0 til 7,0.

**5.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den inneholder et ikke-ionisk isotoniseringsmiddel.

**6.** Sammensetning ifølge krav 5, karakterisert ved at det ikke-ioniske isotoniseringsmiddelet er en sukkeralkohol.

**7.** Sammensetning ifølge krav 5 eller 6, karakterisert ved at vektandelen av det ikke-ioniske isotoniseringsmiddelet er større enn vektdelen av paracetamol.

**8.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den har en osmolaritet på minst 0,25 osmol $l^{-1}$.

**9.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den praktisk talt ikke inneholder noe salt.

**10.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at paracetamolen foreligger i en konsentrasjon på 10,0±5,0 g $l^{-1}$.

**11.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at innholdet av paracetamol etter lagring ved 60 °C i 4 uker minst utgjør 99,0 % av paracetamolen som opprinnelig var inneholdt i sammensetningen.

**12.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den foreligger bruksklar.

**13.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at den har en osmolaritet på høyst 0,36 osmol $l^{-1}$.

**14.** Sammensetning ifølge et av de foregående kravene, karakterisert ved at infusjonsløsningen er klargjort for intravenøs infusjon over et tidsrom på 2 minutter til 24 timer.

**15.** Sammensetning ifølge et av kravene 1 til 14 til behandling av smerte, foretrukket postoperativ smerte.