CONVENTION APPLICATION FOR A PATENT

I/We, ASTRA LAKEMEDEL AKTIEROLLAG, a Swedish Company, of S-151 85 Sodertalje, Sweden,

hereby apply for the grant of a Patent for an invention entitled:

"PROCESS AND PACKAGE FOR STORING OXIDATION-DECOMPOSABLE SUBSTANCES"

which is described in the accompanying complete specification. This application is a Convention application and is based on an application numbered 7709970-3 for a patent or similar protection made in Sweden on 6th September 1977.

Our address for service is care of EDWIN F. WELLINGTON, Patent Attorneys, 457 St. Kilda Road, Melbourne, in the State of Victoria, Commonwealth of Australia.

DATED this 14th day of August, A.D. 1978

ASTRA LAKEMEDEL AKTIEROLLAG
Bevtill Eriksson/Managing Director

To: The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA.
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

In Support of the Convention application made by ASTRA LAKEMEDEL AKTIEBOLAG for a Patent/Patent of Addition for an invention entitled:

"PROCESS AND PACKAGE FOR STORING OXIDATION-DECOMPOSABLE SUBSTANCES"

I, Bertil Eriksson, Managing Director of, ASTRA LAKEMEDEL AKTIEBOLAG, of S-151 85 Sodertalje, Sweden, do solemnly and sincerely declare as follows:

1. I am authorised by ASTRA LAKEMEDEL AKTIEBOLAG, the applicant for the Patent/Patent of Addition, to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made at the Patent Office, Stockholm, Sweden on the 6th day of September 1977 by ASTRA LAKEMEDEL AKTIEBOLAG.

3. LENNART EVEN ERNEROT, of Osjastigen 12, S-151 52 Sodertalje, Sweden, is the actual inventor of the invention and the facts upon which ASTRA LAKEMEDEL AKTIEBOLAG is entitled to make the application are as follows: The Company is the assignee of the actual inventor.

4. The basic application referred to in paragraph 2 of this declaration was the first application made in a Convention country in respect of the invention the subject of the application.

Declared at Sodertalje, Sweden this 14th day of August, 1978

ASTRA LAKEMEDEL AKTIEBOLAG

Bertil Eriksson/Managing Director

To: The Commissioner of Patents, COMMONWEALTH OF AUSTRALIA.
Process and package for storing oxidation-decomposable substances

Astra Lakemedel A.B.
Ernerot, L.S.

Claim

9. Package for the protection of pharmaceutically active solutions containing oxidation-decomposable substances, which solutions are stored in cylindrical ampoules, disposable injection syringes, injection solution flasks and such like units, said package being characterized in comprising an oxygen gas-impervious outer package containing at least one such unit and hydrogen gas and a catalyst which catalyzes in said outer package the reaction of hydrogen and oxygen to water.
Name of Applicant:  ASTRA LAKEMEDEL AKTIEBOLAG

Address of Applicant:  S-151 85 Sodertalje, Sweden

Actual Inventor/z:  LENNART SVEN ERNERJT

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Complete Specification for the invention entitled:
"PROCESS AND PACKAGE FOR STORING OXIDATION-DECOMPOSABLE SUBSTANCES"

The following statement is a full description of this invention including the best method of performing it known to me/us:
The present invention relates to a process and a package for substantially preventing oxidation-decomposition of substances sensitive to oxidation in pharmaceutically active preparations in the form of solutions.

The object of the present invention is to provide for the long-term storage of pharmaceutically active preparations in the form of solutions, which preparations contain substances which are sensitive to oxidation-decomposition.

A further object is to provide for the packing of pharmaceutical solutions in plastic packages, including those cases where the substances present are not so easily decomposed by oxidation, but also where it hitherto has not been practical to store such substances in plastic packages but only in glass-ware packages.

Local-anaesthetic preparations containing adrenaline are examples of preparations which are very sensitive to oxidation, the adrenaline being easily decomposed by oxidation.

Adrenaline is added to local-anaesthetic injectible solutions in order to obtain a contraction of the vessels around the injection site and thereby prevent the local-anaesthetic substance being removed too fast from the injection site. Adrenaline is thus added to reduce blood through-passage in the tissue to be anaesthetized.

Adrenaline is very easily affected by oxygen from the environment and is thereby decomposed to non-active compounds.
In spite of the fact that local-anaesthetic solution containing adrenaline is stored in a cylindrical ampoule of glass or plastic provided with a plunger of rubber in one end and a membrane of rubber in the other, relatively large amounts of air oxygen may pass through into the solution, the adrenaline present being thereby rapidly oxidized. The amount of oxygen which passes into a cylindrical ampoule of said type having a volume of 2 ml is not less than corresponds to 0.5 ml over a two-year period. As the amount of adrenaline is only 2.5-20 μg/ml it will be understood that the adrenaline is very rapidly decomposed.

There is also great demand for long-term storage of local-anaesthetic injectible solutions, particularly at temperatures which are within and above ambient temperature (+22°C).

At the present time there is a need for additives such as sodium pyrosulphite and other preserving agents to be added to the injectible solutions in order to prevent the oxidation of the adrenaline and any noradrenaline or derivatives thereof which may be present in such solutions. There is thus a considerable demand for completely or substantially completely eliminating such additives.

We have now found that it is possible to substantially prevent oxidation-decomposition of oxidation-sensitive substances in pharmaceutically active solutions stored in cylindrical ampoules, disposable injection syringes, injection solution flasks, and such like units, by means of the present invention, which is characterized in that one or more such units is
enclosed in an oxygen-impervious outer package to which is introduced hydrogen and a catalyst which catalyzes therein the reaction of hydrogen and oxygen to water.

A preferred embodiment of the invention is characterized in that the volume of the hydrogen introduced is at least twice the volume of oxygen present in the outer package.

Another preferred embodiment of the invention is characterized in that inert gas is introduced into the package prior to the introduction of hydrogen.

Another preferred embodiment of the invention is characterized in that the package is evacuated, possibly after a preceding introduction of inert gas, prior to the introduction of hydrogen.

Another preferred embodiment of the invention is characterized in that hydrogen is introduced in an amount of up to 8% of the free inner volume of the package.

Another preferred embodiment of the invention is characterized in that the catalyst is palladium, platinum, rhodium, osmium, iridium or ruthenium.

Another preferred embodiment of the invention is characterized in that the pharmaceutically active solution contains a local-anaesthetic compound and a compound selected from the group consisting of adrenaline, noradrenaline and derivatives of them.
Thus the invention provides a package for the protection of pharmaceutically active solutions containing oxidation-decomposable substances, which solutions are stored in cylindrical ampoules, disposable injection syringes, injection solution flasks, and such like units, said package being characterized in comprising an oxygen gas-impervious outer package containing one or more of said units and hydrogen gas and a catalyst which catalyzes in said outer package the reaction of hydrogen and oxygen to water.

A preferred embodiment of the invention is characterized in that the outer package contains an addition of inert gas.

Another preferred embodiment of the invention is characterized in that the outer package consists of a metallic container.

Another preferred embodiment of the invention is characterized in that the outer package consists of a laminate of aluminum foil-plastic foil, which laminate has been sealed via the plastic foil to the formation of a space receiving said units.

Another preferred embodiment of the invention is characterized in that said units contain a local-anaesthetic solution and a compound selected from the group consisting of adrenaline, noradrenaline and derivatives of them.

As inert gas, nitrogen gas and/or carbon dioxide may preferably be used, but obviously other protecting gases, such as argon, may also be considered for such use.
The amount of hydrogen gas has been said above to be desirably up to 8% of the free, inner volume of the outer package. However, the molar amount of hydrogen gas should in each case always be at least twice the residual molar amount of oxygen, that is, the volume of hydrogen gas should be double the volume of oxygen gas in the package in order to obtain a substantially complete reaction of hydrogen and oxygen to water.

Local-anaesthetic compounds of general use, which may be present in the injectible solutions, with an addition of adrenaline, include lidocaine (Xylocaine), bupivacaine (Marcaine), mepivacaine (Carbocaine), and prilocaine (Citanest). Other compounds may also be present, together with the adrenaline.

Suitable catalysts for use in accordance with the invention are the so-called platinum group metals, that is, platinum, palladium, rhodium, osmium, iridium, and ruthenium, which all catalyze the reaction of hydrogen and oxygen to water. The catalyst, which is added in only small amounts, is preferably added together with a carrier such as carbon.

The catalyst may be added to the package in pulverulent form, in tablet form, or bound to a foil shaped carrier. In the latter case, the catalyst may be fastened to the inner side of the package. Also the foil shaped carrier may contain an indicator compound to indicate the possible presence of free oxygen. Methylene blue is such an indicator compound, in changing from blue to white in the absence of oxygen.
The outer package consists of an oxygen-impervious casing, suitably a metallic casing, such as sheet-iron or aluminum foil which has been laminated with a plastic foil so that the plastic foil serves as a sealing member for the outer package. The plastic foils are thereby heat-sealed to each other, using different methods to increase the area of the sealing zone, such as rifling or "waffling" thereof.

The present invention will be described more in detail below:

Ten cylindrical ampoules are provided, made of glass and each containing 1.8 ml of an injection solution, and comprising a cylindrical body somewhat tapered at one end, and each provided in said end with a rubber membrane piercable with an injection needle, and in the other end with a rubber plunger. The injection solution contains 20 mg of lidocaine hydrochloride per ml and adrenaline bitartrate corresponding to 12.5 µg of adrenaline per ml. The cylindrical ampoules are packed in an outer casing consisting of a laminate of aluminum foil-plastic foil. In the outer casing is introduced a nitrogen gas-hydrogen gas mixture (92:8) and 0.1 mg of palladium in the form of 5% Pd on carbon. In spite of the introduction of the nitrogen gas, there is immediately after sealing of the package, minor amounts of oxygen left in the package. A check-up 1 h after, showed no analyzable amounts of free oxygen were present in the package.

In forced storing tests, free oxygen has not in any case been able to be analyzed, and the amount of adrenaline has been constant, 12.5 µg, all the time.
By means of the present invention, a further advantage that can be achieved is that the units containing the injectible solution containing adrenaline, such as cylindrical ampoules, disposable injection syringes, and injection solution flasks or so-called vials, need not necessarily be made of glass but can be made of another material which is not oxygen impervious *per se* as glass is, provided that other criteria for the storage of the injection solutions are fulfilled.

The matter contained in each of the following claims is to be read as part of the general description of the present invention.
The claims defining the invention are as follows:

1. Process for substantially preventing oxidation-decomposition of substances sensitive to oxidation and present in pharmaceutically active preparations in the form of solutions stored in cylindrical ampoules, disposable injection syringes, injection solution flasks and such like units, characterized in that one or more such units is enclosed in an oxygen gas-impervious outer package to which is introduced hydrogen gas and a catalyst which catalyzes therein the reaction of hydrogen and oxygen to water.

2. Process according to claim 1, characterized in that the volume of the hydrogen gas introduced is at least twice the volume of oxygen gas present in the outer package.

3. Process according to claim 1 or 2, characterized in that an inert gas is introduced into the package prior to the introduction of hydrogen gas.

4. Process according to claim 1 or 2, characterized in that the package is evacuated prior to the introduction of hydrogen gas.

5. Process according to claim 4, characterized in that an inert gas is introduced prior to the evacuation and the introduction of hydrogen gas.

6. Process according to any one of claims 1 to 5, characterized in that hydrogen gas is introduced in an amount that is up to 8% of the inner free volume of the package.

7. Process according to any one of claims 1 to 6, characterized in that the catalyst is selected from the group
consisting of platinum, palladium, rhodium, osmium, iridium, and ruthenium.

8. Process according to one of claims 1 to 7, characterized in that the pharmaceutical containing unit contains a local-anaesthetic compound and a compound selected from the group consisting of adrenaline, noradrenaline and derivatives thereof.

9. Package for the protection of pharmaceutically active solutions containing oxidation-decomposable substances, which solutions are stored in cylindrical ampoules, disposable injection syringes, injection solution flasks and such like units, said package being characterized in comprising an oxygen gas-impervious outer package containing at least one such unit and hydrogen gas and a catalyst which catalyzes in said outer package the reaction of hydrogen and oxygen to water.

10. Package according to claim 9, characterized in that the volume of hydrogen gas is at least twice the volume of oxygen gas.

11. Package according to claim 9 or 10, characterized in that the outer package further comprises inert gas.

12. Package according to any one of claims 9 to 11, characterized in that the catalyst is selected from the group consisting of platinum, palladium, rhodium, osmium, iridium, and ruthenium.
13. Package according to any one of claims 9 to 12, characterized in that said units contain a local-anaesthetic solution and a compound selected from the group consisting of adrenaline, noradrenaline and derivatives of these.

14. Package according to any one of claims 9 to 13, characterized in that the outer package consists of a metal container.

15. Package according to claim 14, characterized in that the outer package consists of a laminate composed of aluminium foil-plastic foil, which laminate has been sealed via the plastic foil for the formation of a space receiving said units.

16. Process according to claim 1, substantially as described herein.

17. Package according to claim 9, substantially as described herein.

DATED this 24th day of August, A.D. 1978

ASTRA LAKE MEDEL AKTIEBOLAG,
By its Patent Attorney,

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EDWIN F. WELLINGTON
Fellow of the Institute of Patent Attorneys of Australia, (Inc.)