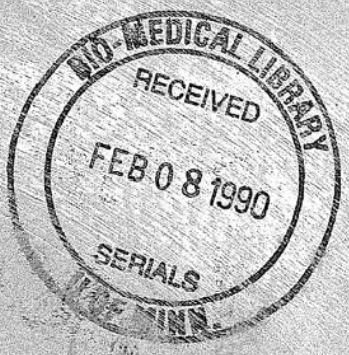
Volume 25 Supplement 1 1989 ISSN 0277-5379

EUROPEAN JOURNAL OF CANCER & CLINICAL ONCOLOGY

Official Journal for
European Organization for Research and Treatment of Cancer (EORTC)
European Association for Cancer Research (EACR)

25th Anniversary Volume

Proceedings of the Ondansetron Symposium Queen Elizabeth II Conference Centre, London 30 June 1989



European Journal of Cancer & Clinical Oncology

Subventionné par le Ministère de la Communauté Francophone de Belgique
Met de steun van de Ministerie van de Vlaamse Gemeenschap

Publishing & Advertising Offices: Headington Hill Hall, Oxford OX3 0BW (Oxford 64881)

Subscription rates (1990) (including postage and insurance) Annual institutional subscription rate (1990) DM 1490.00. 2 year institutional rate (1990/91) DM 2831.00. Personal subscription rate for those whose library subscribes at the regular rate (1990) DM 220.00. Prices are subject to change without notice. Twelve issues, published monthly. Subscription enquiries from customers in North America should be sent to: Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523, U.S.A., and for the remainder of the world to Pergamon Press plc, Headington Hill Hall, Oxford OX3 0BW, U.K.

The Item-Fee Code for this publication is: 0277-5379/89$3.00 + 0.00

Eur J Cancer Clin Oncol, Vol. 25, Suppl. 1, pp. S67–S69, 1989
Printed in Great Britain

0277–5379/89 $3.00 + 0.00

Pharmaceutical Development of Ondansetron Injection

R.E. LEAK and J.D. WOODFORD

Glaxo Group Research Ltd., Park Road, Ware, Hertfordshire, SG12 0DP, U.K.

Abstract – *Ondansetron injection is an aqueous solution containing ondansetron base as the hydrochloride dihydrate. The pH of the injection was selected to achieve good physical and chemical stability. The shelf life is 3 years when stored below 30°C, protected from light.*

Ondansetron injection may be diluted for administration by slow intravenous injection or infusion and is compatible with several intravenous infusion fluids. In addition, specific concentrations of cisplatin, 5-fluorouracil, carboplatin, etoposide, ceftazidime, cyclophosphamide and doxorubicin are compatible when administered via a giving set delivering ondansetron by infusion.

PRESENTATIONS

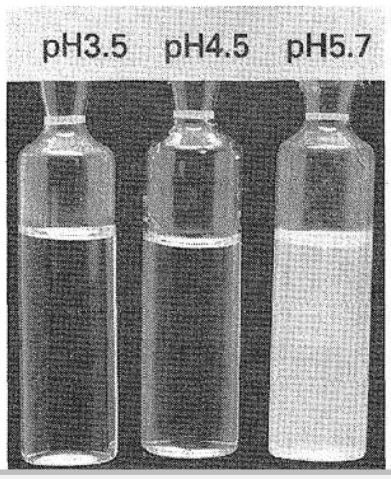
ONDANSETRON injection is an aqueous solution containing 2 mg/ml ondansetron base as the hydrochloride dihydrate. Sodium citrate and citric acid monohydrate are added to buffer the solution at pH 3.5 and sodium chloride is added to achieve isotonicity. The injection solution is filled into ampoules to provide dose volumes of 2 ml and 4 ml, equivalent to 4 mg and 8 mg of ondansetron respectively, and is terminally sterilised by autoclaving.

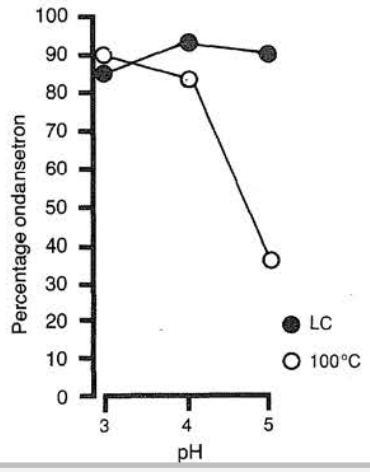
STABILITY

The pH of the injection was selected to achieve good physical and chemical stability. The natural pH of solutions of ondansetron hydrochloride dihydrate is about 4.5, depending on the ondansetron concentration. If pH is increased (e.g. by the addition of alkali), a precipitate of ondansetron free base is observed at about pH 5.7 (Fig. 1), therefore requiring the pH of the injection solution to be maintained below this value.

The stability of a 2.5 mg/ml solution of ondansetron buffered at pH 3, 4 and 5 stored at elevated temperature and in intense light in a light cabinet is given in Figure 2. The results show that the solution is more stable to storage at elevated temperature at pH 3 and 4 than at pH 5, and that there is little difference in the stability of the solution in this pH range to intense light.

These data indicate that a pH of 3.5 should achieve the required physical and chemical stability for ondansetron injection. In practice ondansetron injections at pH 3.5 have been shown to be





very stable. An injection of the same formulation as that proposed for marketing but with a concentration of ondansetron of 2.5 mg/ml showed no change in ondansetron concentration, pH or drug-related impurities when stored for 3 years at 30°C. Stability data to date on ondansetron injection 2 mg/ml show no change in ondansetron concentration (Fig. 3), pH or drug-related impurities for the injection stored for 1 year at 37°C. Ondansetron injection is unstable when stored under intense light, but is stable for about a month in daylight supplemented with fluorescent lighting (Fig. 3).

The shelf life of ondansetron injection is 3 years when stored below 30°C, protected from light.

ANALYTICAL METHODS

The ondansetron content of ondansetron injection is determined by the same HPLC method as is used for the assay of ondansetron tablets [1].

Figure 4 shows a chromatogram of ondansetron injection. The method gives precise and accurate results for the ondansetron content of ondansetron injection.

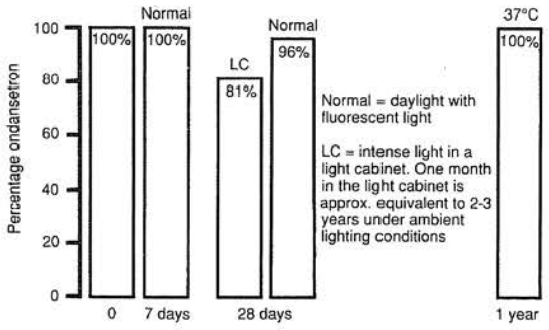
COMPATIBILITY

Compatibility with infusion fluids

Ondansetron may be administered by slow intravenous injection or by intravenous infusion by diluting ondansetron injection with an appropriate volume of intravenous infusion fluid.

Ondansetron injection is compatible with the following intravenous infusion fluids:

- Sodium Chloride Intravenous Infusion BP 0.9% w/v
- Glucose Intravenous Infusion BP 5% w/v
- Mannitol Intravenous Infusion BP 10% w/v
- Ringers intravenous infusion
- Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP
- Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.



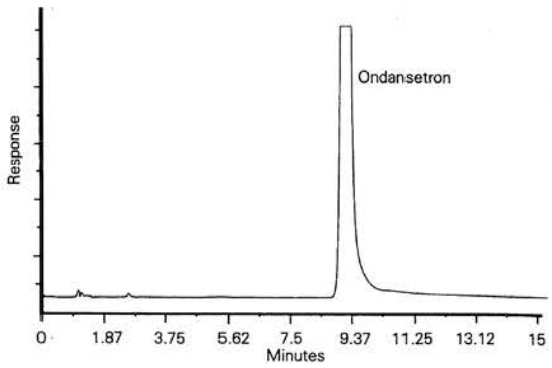


Fig. 4. HPLC chromatogram of ondansetron injection.

Compatibility was tested by adding 8 mg ondansetron (4 ml of ondansetron injection) to 500 ml PVC infusion bags of each infusion. PVC giving sets were attached and primed and the test system stored under ambient conditions of temperature and light. Samples were taken for analysis via the giving set after 24 h storage and from the bags after 7 days storage. These showed no significant change in ondansetron concentration, drug-related impurities or numbers of particles for all of the infusions tested. Duplicate dilutions of the injection in 500 ml infusion bags stored at 4°C, protected from light, were also physically and chemically stable for 7 days.

In addition, for Sodium Chloride Intravenous Infusion BP 0.9% w/v and Glucose Intravenous Infusion BP 5% w/v, 8 mg of ondansetron was added to 100 ml infusion bags and stored under ambient conditions or at 4°C. These solutions (sampled from the infusion bag) were also shown to be stable for 7 days.

These results demonstrate that ondansetron is compatible with the infusion fluids tested and with PVC infusion bags and giving sets.

Preparation of dilutions of ondansetron injection in advance of use. Provided dilutions of ondansetron injection are prepared under appropriate aseptic conditions, they may be prepared in advance of use. Dilutions of ondansetron injection in compatible infusion fluids are stable for 7 days at 4°C or at room temperature (<25°C) exposed to ambient light.

Containers for dilutions. The above compatibility tests were performed in PVC infusion bags. It is considered that adequate compatibility would also be conferred on dilutions in polyethylene infusion bags or Type 1 glass bottles since these are known to be more inert than PVC.

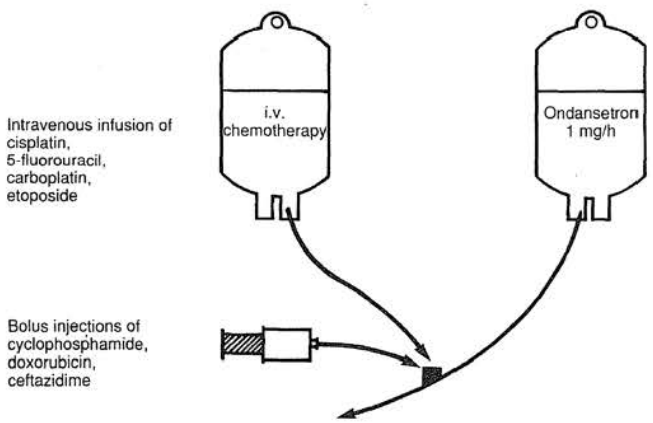


Fig. 5. Co-administration of ondansetron infusion and other therapeutic agents.

days at 4°C or at room temperature in polypropylene neoprene rubber syringes (e.g. Plastipak, Becton Dickinson & Co. Ltd.) fitted with syringe caps (e.g. Universal Plug, Vygon).

Compatibility with other therapeutic agents

Ondansetron may be administered at 1 mg/h by intravenous infusion from an infusion bag or syringe pump with an attached giving set. Other drugs, such as anticancer agents or antibiotics, may need to be co-administered intravenously via the Y-site of the giving set delivering ondansetron.

Other medication should *not* be mixed directly with ondansetron injection in an infusion bag, syringe or any other administration system.

The drugs may be administered by intravenous infusion or bolus injections as appropriate. Those drugs which are compatible with ondansetron are shown in Figure 5, along with their route of administration.

Doses of anticancer agents are variable and therefore extremes of concentrations were evaluated where appropriate. The compatibility data support the co-administration of the following concentration/doses of the drugs listed in Figure 5.

The following drugs may be administered via the Y-site of the ondansetron giving set delivering ondansetron at 1 mg/h for ondansetron concentrations of 16 to 160 μg/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively).

Cisplatin. Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over 1–8 h.

5-fluorouracil. Concentrations up to 0.8 mg/ml (e.g. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml/h (500 ml/24 h). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin. Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over 10 min to 1 h.

Etoposide. Concentrations in the range 0.144 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over 30 min to 1 h.

Cyclophosphamide. Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately 5 min.

Doxorubicin. Doses in the range 10 mg to 100 mg reconstituted with Water for Injections BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 min.

Ceftazidime. Doses in the range 250 mg to 2 g reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime) and given as an intravenous bolus injection over approximately 5 min.

PHARMACEUTICAL PRECAUTIONS

Ondansetron injection should be protected from light, and should only be admixed with those infusion solutions which are recommended.

Ondansetron injection should not be mixed in the same syringe or infusion as any other medication, and it must not be reautoclaved.

REFERENCE