

TCH-023 LIQUID ORAL FORMULATIONS OF PROPRANOLOL HYDROCHLORIDE FOR THE TREATMENT OF INFANTILE HAEMANGIOMAS

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¹P Horak, ¹S Klovřzova, ²J Malis, ³Z Sklbalova. ¹University Hospital Prague-Motol, Hospital Pharmacy, Praha 5, Czech Republic; ²University Hospital Prague-Motol, Department of Pediatric Hematology and Oncology, Praha 5, Czech Republic; ³Charles University Faculty of Pharmacy, Department of Pharmaceutical Technology, Hradec Kralove, Czech Republic

Background Oral propranolol has been found successful in the treatment of infantile haemangiomas. Paediatric dosage forms of propranolol are not commercially available in our country.

Purpose To develop an extemporaneous oral dosage form of propranolol appropriate for children from 14 days to 24 months of age in hospital and an ambulatory care setting and to determine its stability. The requirement for minimum excipients for the safety of targeted age group was considered.

Materials and Methods A solution of propranolol 2 mg/ml was prepared from the substance. We used citric acid or citrate-phosphate buffer to achieve the optimum stability of propranolol (pH about 3) and simple syrup to mask the bitter taste of the active ingredient. Two formulations (depending on the patient's age) were developed – one using sodium benzoate as preservative and one preservative-free. The preservative-free solution was prepared aseptically with a limited expiry date. The stability of the preserved solution was evaluated for 180 days at room and reduced (2–8°C) temperatures using a validated HPLC method and pH measurements.

Results The formulation preserved with sodium benzoate was stable at both temperatures for 180 days. The concentration of propranolol varied between 98.2–102.5%, the pH value did not change significantly. The efficacy of antimicrobial preservation (Ph.Eur., 5.1.3) was proven for sodium benzoate 0.05%. A risk assessment of the formulation was undertaken (<100) and an appropriate quality assurance system was developed. A glass bottle with an oral syringe enabled the dose of propranolol to be given with flexibility and accuracy.

Conclusions The preparation of propranolol solution in the pharmacy enabled 23 paediatric patients aged 0.6–20.9 months to be treated successfully for haemangiomas by our hospital.

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No conflict of interest.

TCH-024 LONG-TERM STABILITY OF INDOMETHACIN 0.2 MG/ML READY-TO-USE SOLUTION FOR INTRAVENOUS USE

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R Moudry, S Hornstein, M Fehr-Bigger, S Guyer. Kantonsspital Graubünden, Institute for Hospital Pharmacy, Chur, Switzerland

Background Indomethacin 1 mg is used in premature infants to close the patent ductus arteriosus. The commercial product Indocid PDA is no longer available in Switzerland. Nevertheless, on our paediatric ward there is a great need for an intravenous indomethacin solution that can be used at a dose of 0.1–0.2 mg/kg body weight.

Purpose To produce a parenteral ready-to-use solution containing 0.2 mg/ml indomethacin and to determine the long-term stability using a stability indicating high-pressure liquid chromatography (HPLC) method.

Materials and Methods Liometacen, containing 50 mg sterile indomethacin (as meglumine salt), was reconstituted with 2 ml water for injection and then diluted with 250 ml NaCl 0.9% to a final indomethacin concentration of 0.2 mg/ml. Finally, a 5 ml indomethacin solution was filled into 10 ml sterilised brown glass vials. The entire process took place under aseptic conditions. Sterility testing was performed before final batch release.

The vials were stored for up to 18 months frozen at –20°C, at 2–8°C or at room temperature, and the solutions were assessed by HPLC for indomethacin and its degradation products.

Results Indomethacin solutions were submitted to conditions of oxidative or heat degradation, and the HPLC method was found to indicate stability.

The stability testing revealed that the solutions retained at least 95% of their initial indomethacin concentration when they were stored at room temperature for 12 days or at 2–8°C for 23 days.

In contrast, when the solutions were stored in a deep-freezer, they were stable for at least 18 months. During this time, no degradation of indomethacin occurred and the indomethacin concentration remained stable.

Conclusions Indomethacin solutions may be prepared in advance and stocked for at least 18 months at –20°C. After thawing they can be kept at room temperature for 7 days or alternatively at 2–8°C for 14 days. This procedure is used successfully in our hospital for the treatment of the patent ductus arteriosus.

No conflict of interest.

TCH-025 LONG-TERM STUDY OF THE FORMATION OF AGGREGATES IN UNDILUTED BEVACIZUMAB 25 MG/ML

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¹J Hernández-Jiménez, ²A Salmerón-García, ¹N Navas-Iglesias, ¹A Martínez-Ortega, ³J Cabeza-Barrera, ¹LF Capitán-Vallvey. ¹University of Granada, Analytical Chemistry, Granada, Spain; ²Baza Hospital, Hospital Pharmacy Unit, Baza, Spain; ³University Hospital San Cecilio, Hospital Pharmacy Unit, Granada, Spain

Background Bevacizumab, the active substance of Avastin®, is a humanised monoclonal antibody that acts as angiogenesis inhibitor, a drug that slows the growth of new blood vessels. It is used to treat several cancers, including colorectal, lung, breast, kidney and ovarian. Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells.

Purpose To evaluate the stability of bevacizumab 25 mg/ml in solution for infusion, in terms of the formation of aggregates once the vial was open. The study was carried out for 15 days since the manufacturer only indicates chemical and physical in-use stability for up to 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection, if the solution was prepared in validated aseptic conditions. The manufacturer also indicates that the prepared solution should not be frozen.

Materials and Methods The study of the formation of the aggregates was carried out by using a size exclusion high performance liquid chromatography method with diode array detection method (SE-HPLC-DAD). Two different storage conditions, i.e. refrigerated at 4°C and frozen at –20°C were maintained for 15 days. Samples were characterised by chromatographic analysis immediately after the vial was opened. These chromatographic data were compared with those obtained on subsequent days. A stress study was also conducted.

Results Analysis of freshly-prepared samples enabled us to characterise bevacizumab chromatographically by SE-HPLC-DAD. In the corresponding chromatograms monomers were clearly detected (main peak in the chromatogram) at 7.7 ± 0.1 min of retention