

## A new paediatric formulation of valaciclovir: development and bioequivalence assessment

Diane ET Bastiaans<sup>1</sup>, Carli M. Wilmer<sup>1</sup>, Angela P.H. Colbers<sup>1</sup>, Claudia A.W. Heijens<sup>2</sup>, Kirsten Velthoven-Graafland<sup>1</sup>, Oscar S.N.M. Smeets<sup>3</sup>, Nicole Vink<sup>1</sup>, Veroniek E.M. Harbers<sup>4</sup>, Adilia Warris<sup>5</sup>, David M. Burger<sup>1</sup>

1. Department of Pharmacy, Radboud University Medical Center, Geert Grooteplein-Zuid 10, 6525 GA, Nijmegen, The Netherlands.
2. Department of Pharmacy, Zuyderland Medical Center, Henri Dunantstraat 5, 6419 PC, Heerlen, The Netherlands,
3. Royal Dutch Pharmacists Association, Alexanderstraat 11, 2514 JL, The Hague, The Netherlands.
4. Clinical Research Center Nijmegen, Radboud University Medical Center, Philips van Leijdenlaan 15, 6525 EX Nijmegen, The Netherlands.
5. Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK

A paediatric formulation of valaciclovir with acceptable palatability, good pharmaceutical quality and stability and with the possibility of flexible dosing is currently not available. A preparation of valaciclovir liquid as described in the FDA label information was found not to be adequate for use in daily practice, because of the need to use crushed tablets and the short shelf life.<sup>1</sup> Results of a small paediatric study found a mean relative bioavailability of this liquid compared to the tablets of 91.1% (SD, 33.1%), but this was not investigated following the regulatory guidance for bioequivalence testing.<sup>2</sup> The aim of this study was to develop a new paediatric formulation and to assess the bioequivalence of this new formulation compared to the brand named valaciclovir tablets.

An oral liquid was developed because this is generally considered acceptable for use in infants and young children.<sup>3</sup> Dosing accuracy, use of non-toxic excipients, palatability and good pharmaceutical stability for an acceptable period of time were all taken into account during the development. A solution was developed with 20 mg/mL valaciclovir (as valaciclovir HCl.1 H<sub>2</sub>O) and glycerol (42.5%), citric acid, disodium hydrogenphosphate and water as excipients, with pH 3.5 as target. The new formulation has a shelf-life of at least six months. The preparation method and developmental aspects of the new formulation has been included in the Formulary of the Dutch Pharmacists (FNA) and is freely available upon request.

Bioequivalence of the new formulation compared to the innovator product was tested in a randomized, single-dose (500 mg), open label, two-period crossover, phase-I trial in 16 fasting healthy adult volunteers, according to the European Medicines Agency (EMA) guideline for investigation of bioequivalence.<sup>4</sup> Medical ethical approval for conduction of the trial was obtained (CMO Arnhem-Nijmegen Radboud University Medical Center; NCT01689285). Rate and extent of absorption was determined by three pharmacokinetic parameters: area under the plasma concentration time curve (AUC), maximum plasma concentration (C<sub>max</sub>), and time to maximum plasma concentration (T<sub>max</sub>). These were calculated using non-compartmental analysis (WinNonlin/Phoenix® v6.4. Pharsight Corporation, USA). Subjects in the bioequivalence assessment had a median age of 31.5 years (range 19-55), body mass index of 23.7 (range 18.8-29.9) and 9 were male. Adverse events possibly related to the study drug were reported by two subjects. The adverse

events were mild and both subjects recovered from the adverse events within 24 hours after onset of the symptoms. The geometric mean pharmacokinetics parameters are shown in Table 1 and mean plasma concentration-time profiles are depicted in Figure 1. The new valaciclovir solution met the criteria for bioequivalence regarding the AUC<sub>0-12</sub>. However, the upper limit of the 90%CI of the ratio for C<sub>max</sub> was just above the 125% criterion. Because of the mild toxicity profile of (val)aciclovir, it is not expected that the slightly higher C<sub>max</sub> will result in more adverse events.

With the results of this study it can be concluded that the newly developed valaciclovir solution can be used as an alternative formulation for (paediatric) patients who experience difficulties with the administration of valaciclovir tablets.

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### References

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**Table 1** Geometric mean values of aciclovir pharmacokinetic parameters

Parameter	Test (solution) (95%CI)	Reference (tablet) (95%CI)	Ratio T/R (%) (90%CI)
C <sub>max</sub> (mg/L)	3.63 (3.27 to 4.02)	2.98 (2.59 to 3.44)	121 (110 to 133)
AUC <sub>0-12</sub> (h*mg/L)	10.6 (9.56 to 11.7)	9.96 (8.71 to 11.4)	106 (100 to 112)
AUC <sub>0-infinity</sub> (h*mg/L)	11.0 (9.95 to 12.2)	10.4 (9.07 to 12.0)	-
Residual area (%)	3.9 (2.9 to 5.1)	3.5 (2.3 to 5.3)	-
T <sub>½</sub> (h)	2.75 (2.50 to 3.02)	2.58 (2.23 to 2.98)	-
T <sub>max</sub> (h) <sup>#</sup>	0.75 (0.75 to 1.44)	1.25 (1.00 to 1.94)	-

<sup>#</sup>T<sub>max</sub>: median value and interquartile range

**Figure 1** Mean (+ SD) plasma concentration-time profile of the new valaciclovir solution and the reference formulation (tablet) after administration of 500 mg valaciclovir.

