

Direct Healthcare Professional Communication regarding serious adverse reactions following off-label use of Vistide

12th January 2011

Dear Health Care Professional

Summary

- Vistide is formulated for intravenous infusion only and must not be administered by other methods including intraocular injection or topically.
- An increased number of adverse reactions are associated with off-label use.
- There has been an increase in the use of Vistide in unapproved indications, and/or routes of administration.
- The safety and efficacy of Vistide in diseases other than CMV retinitis in adults with AIDS has not been demonstrated.

Further information on the safety concern

Gilead Sciences and the European Medicines Agency are writing to remind you that in the European Union, Vistide (cidofovir) is only approved for use in cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) and without renal dysfunction.

An increased use of Vistide in unapproved indications and/or routes of administration, including use in a number of potentially life-threatening viral infections, has been seen from postmarketing reports.

During the period between 23 April 2009 and 22 April 2010, 87% of 46 adverse event reports received by the company, involved the use of Vistide either in an unapproved indication or via an unapproved route of administration.

The most frequent and serious adverse reactions reported for Vistide in off-label indications and routes of administration were renal toxicity, ocular toxicity and neutropenia consistent with the safety profile of Vistide.

The majority of adverse ocular events were associated with intraocular administration of Vistide. In addition, severe erythema, painful erosions and renal toxicity have been reported following topical application of Vistide, after reformulation as a cream or ointment.

The reports of renal toxicity following topical administration of Vistide suggest that topical application of Vistide does not prevent a patient experiencing systemic toxicities associated with the product.

Lack of therapeutic effect was also frequently reported for patients receiving Vistide for unapproved indications or routes of administration. In some cases, involving the treatment of serious and potentially life-threatening conditions, the lack of effect was fatal.

In summary, the benefit-risk profile of Vistide in the treatment of diseases other than CMV retinitis in adults with AIDS, is not established.

The Vistide Summary of Product Characteristics (SPC) and package leaflet have been updated to remind healthcare professionals of the approved indication. Important safety information from the Summary of Product Characteristics for Vistide is provided in Annex I to this letter.

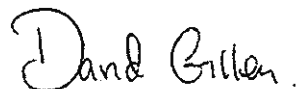
Call for reporting:

If you become aware of any adverse reactions in association with the use of Vistide, please report promptly to the Medicines and Healthcare products Regulatory Agency (MHRA) using a Yellow Card available directly from the MHRA, FREEPOST YELLOW CARD or electronically via the MHRA website, www.yellowcard.gov.uk, and to the company directly at Gilead via e-mail to csafety@gilead.com or by telephone +44 1223 897500 in the usual way.

For further information or a complete copy of the current Vistide SPC, please contact:

Medical Information
Gilead Sciences Limited
Flowers Building
Granta Park
Great Abington
Cambridge
CB21 6GT
Tel. + 44 (0) 1223 897555
ukmedinfo@Gilead.com

Yours sincerely,



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Annex I

Important safety information associated with Vistide and described within the Summary of Product Characteristics (SPC) includes:

Section 4.4 Special warnings and precautions for use

Vistide is formulated for intravenous infusion only and must not be administered by other methods including intraocular injection or topically. Vistide should be infused only into veins with adequate blood flow to permit rapid dilution and distribution.

The safety and efficacy of Vistide has not been demonstrated in diseases other than CMV retinitis in adults with AIDS.

Renal insufficiency/Haemodialysis

Treatment with Vistide must not be initiated in patients with creatinine clearance ≤ 55 ml/min, or $\geq 2+$ proteinuria (≥ 100 mg/dl), as the optimum induction and maintenance doses for patients with moderate to severe renal impairment are not known. The efficacy and safety of cidofovir in such conditions has not been established.

High flux haemodialysis has been shown to reduce the serum levels of cidofovir by approximately 75%. The fraction of the dose extracted during haemodialysis is $51.9 \pm 11.0\%$.

Nephrotoxicity

Dose-dependent nephrotoxicity is the major dose-limiting toxicity related to administration of cidofovir (see section 4.8). The safety of cidofovir has not been evaluated in patients receiving other known potentially nephrotoxic agents (e.g. tenofovir, aminoglycosides, amphotericin B, foscarnet, intravenous pentamidine, adefovir and vancomycin).

Vistide should not be administered concurrently with medicinal products containing tenofovir disoproxil fumarate due to the risk of Fanconi syndrome (see section 4.5 of the SPC).

It is recommended to discontinue potentially nephrotoxic agents at least 7 days before starting cidofovir.

Patients treated at 3.0 mg/kg, 5.0 mg/kg or 10 mg/kg without concomitant probenecid developed evidence of proximal tubular cell injury, including glycosuria, and decreases in serum phosphate, uric acid and bicarbonate, and elevations in serum creatinine. The signs of nephrotoxicity were partially reversible in some patients. Concomitant use of probenecid is essential for reducing the pronounced nephrotoxicity of cidofovir to an extent that results in an acceptable benefit/risk balance of cidofovir therapy.

Ocular events

Patients receiving cidofovir should be advised to have regular follow-up ophthalmologic examinations for possible occurrence of uveitis/iritis and ocular

hypotony. In case of uveitis/iritis cidofovir should be discontinued if there is no response to treatment with a topical corticosteroid or the condition worsens, or if iritis/uveitis reoccurs after successful treatment.

Other

Cidofovir should be considered a potential carcinogen in humans (see section 5.3 of the SPC).

Section 4.8 Undesirable effects

Reports of renal failure (plus events possibly caused by renal failure, e.g. blood creatinine increased, proteinuria, glycosuria) received during post-marketing surveillance include some which were fatal. Cases of acute renal failure have been reported after only one or two doses of cidofovir.