Miller, Diane M. (CDC/NIOSH/EID)

From: willi.suter@novartis.com
Sent: Monday, September 17, 2007 9:19 AM
To: NIOSH Docket Office (CDC)
Cc: philip.bentley@novartis.com; william.kluwe@novartis.com; rudolf.bechter@novartis.com
Subject: 105 - HazDrug Update Comments
Attachments: NIOSH mutagenicity Trileptal and Gleevec final.doc

Dear Sir,

Novartis has reviewed your

List of hazardous drugs (Appendix A) for the NIOSH Alert on Hazardous Drugs
NIOSH Docket #105

Novartis does not agree with the classification of Trileptal and Gleevec as being genotoxic. I attach a summary of our internal data and a reasoning why we belief that neither of this two drug should be labelled as genotoxic.

We would strongly appreciate if you could reconsider your labelling of these two drugs.

Yours sincerely

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NIOSH alert on hazardous drugs NIOSH Docket #105

The results of the mutagenicity studies conducted by Novartis for their drugs Trileptal and Gleevec are summarized below. Using the weight of evidence approach proposed by the US FDA to analyze mutagenicity data [1] it is concluded that neither Trileptal nor Gleevec is genotoxic.

1) Gleevec

Gleevec caused chromosome damage in CHO cells only at the highest concentration tested, 125 μg/ml, in the presence of S9. This concentration was strongly cytotoxic as indicated by the mitotic indices of 41.6%, 44.4% and 49.0% of the concurrent solvent control values (i.e., all greater than 50% mitotic inhibition) observed under these test conditions. At the next lower concentration (62.5 μg/ml; mitotic indices 55.6%, 89.8%, 75.9%) Gleevec did not induce any changes in the frequencies of cells with chromosomal aberrations, which indicates that the structural chromosome damage observed at the highest concentration was most likely an indirect effect due to cytotoxicity. No effects were observed in the absence of S9. The mouse lymphoma tk and V79 hprt assays were negative. In rats Gleevec neither induced chromosomal damage in the bone marrow nor in the liver nor did Gleevec induce DNA strand breaks in the 5 tissues analyzed in the in vivo comet assay. The plasma levels were not assessed as part of the genotoxicity studies, but the Cmax, based on toxicokinetic data from other studies, was estimated to be close to 100 μg/ml, which is in the concentration range assessed in the mammalian in vitro studies. Thus, both in vivo tests conducted to investigate genotoxicity in the liver (liver micronucleus test, comet assay) and the mouse lymphoma assay performed in the presence of S9 did not confirm the positive result observed in CHO cells in the presence of S9. In addition both the Ames test and the V79 HPRT assay were negative.

In conclusion, applying the weight of evidence concept for evaluation of the data presented, Gleevec is considered not genotoxic.

Table 1 Gleevec Genotoxicity Data

Study type	Dose range	Finding	Comments
Ames test (2 studies)	30.9 – 5000 μg/plate ± S9	Negative	
HPRT gene mutation in V79 Chinese hamster cells	7.41 – 200 μg/mL + S9 0.74 – 20 μg/mL - S9	Negative Negative	
Thymidine kinase in Mouse lymphoma cells	0.98 – 62.5 μg/mL + S9 1.56 – 50 μg/mL - S9	Negative Negative	
Chromosomal aberration in CHO cells	31 – 125 μg/mL + S9 1.5 – 12.5 μg/mL - S9	Positive at 125 μg/ml Negative	Positive findings with S9 at the highest concentration only, mitotic indices below 50% in all 3 cases
Rat bone marrow micronucleus test (i.v.)	25, 50 & 100 mg/kg	Negative	
Rat liver micronucleus test (oral)	180 mg/kg given daily from day 1 to 13; 500 and 1000 mg/kg, given on days 14 and 16; partial hepatectomy on day 15; sampling 48 and 72 h after partial hepatectomy	Negative	Decrease in mitotic index indicating toxicity
Rat comet assay (liver, kidney, urinary bladder, preputial gland, clitoral gland)	500 and 1000 mg/kg given twice 21 h apart; sampling 3 h after 2nd treatment	Negative	Various clinical signs indicating toxicity

2) Trileptal

Trileptal induced polyploidy in mammalian cell lines (CHO, V79), which is not considered to be a genotoxic effect, since it does not involve a direct interaction between the test compound and the DNA. Furthermore, polyploidy is frequently observed in mammalian cell lines in vitro and is generally not reproduced in vivo [2]. An increase in structural chromosome aberrations was observed only in one arm of the study conducted in CHO cells, i.e. after 39 h treatment in absence of S9, and at concentrations which induced high frequencies of polyploid cells. It is, therefore, concluded that the clastogenic effect observed after prolonged treatment is an indirect effect of the disturbed chromosome separation.

Trileptal was tested in 3 Ames studies. Study 2 provided a positive result in strain TA100 in the absence of S9, whereas studies 1 and 3 provided clear negative results. It is not known what caused this effect; a batch effect could be excluded. Since Trileptal was negative in two other independent studies conducted some years before and after the positive experiments, it was most likely an unknown variation in the test conditions used at the time when the study was conducted, which caused the positive result in study 2.

Apart from the positive results discussed above Trileptal did not show any mutagenic effects in the other 2 mammalian in vitro studies, which included a chromosomal aberration test in V79 cells, and in the 5 in vivo cytogenetic studies conducted. The Ames positive result was not confirmed in the HPRT gene mutation assay in V79 cells.

In conclusion, applying the weight of evidence concept for the evaluation of the data presented, Trileptal is not considered genotoxic

Table 2 Trileptal Genotoxicity Data

Study type	Dose range	Finding	Comments
Ames test	25-2025 μg/plate	negative	
Ames test including Escherichia coli WP2 uvrA	39.1-5000 μg/plate	Positive, weak increase by factors of up to 2.5 times control in strain TA100, -S9 at 312.5 μg/plate; negative under all other test conditions	
Ames test	8-5000 μg/plate	negative	
HPRT gene mutation assay in Chinese hamster lung V79 cells	2.5-500 μg/mL	negative	
Chromosomal aberration assay in Chinese hamster ovary (CHO) cells	7.81-500 μg/mL	polyploidy, weak clastogenicity after 42 h treatment, -S9; no effects after shorter treatments or +S9	Increased structural chromosome damage after 42 h treatment at concentrations that clearly increased the number of polyploid cells; negative under all other test conditions
Chromosomal aberration assay in Chinese hamster lung (V79) cells	5-500 μg/mL	Polyploidy; no structural chromosome damage	
In vivo chromosomal aberration assay in Chinese hamster bone marrow cells	510-2040 mg/kg p.o. 2 treatment on consecutive days, colcemide injected 2 h after 2nd dose; tissue sampling 4 h later	negative	
In vivo nuclear anomaly test in Chinese hamster bone marrow cells	510-2040 mg/kg p.o. 2 treatments on consecutive days, tissue sampling 24 h after the 2nd application	No evidence for clastogenic or aneugenic effects	
In vivo micronucleus test in rat bone marrow	625-2500 mg/kg p.o. 1 treatment; highest dose group sampled 16, 24 and 48 h after treatment; 2 lower dose groups sampled 24 h after treatment	negative	
In vivo chromosomal aberration assay in mouse germinal epithelium (spermatogonia)	210-840 mg/kg p.o. 5 treatments on consecutive days; day 5, tissue sampling 3 h after colcemide injection	negative	
In vivo chromosomal aberration assay in mouse germinal epithelium (spermatocytes)	420-1680 mg/kg p.o. treatment on days 0, 2, 3, 5 and 9; day 12, tissue sampling 3 h after colcemide injection	negative	

References

[1] Guidance for Industry Recommended Approaches to Integration of Genetic Toxicology Study Results, Draft guidance, CEDR, November 2004
[http://209.85.129.104/search?q=cache:DDnDdz5OD4AJ:www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0493-gdl0001.pdf+FDA+and+%22weight+of+evidence%22+and+%22genetic+toxicology%22&hl=de&ct=clnk&cd=5&gl=ch]

[2] De Mitchell IG, Lambert TR, Burden M et al. (1995), Is polyploidy an Important genotoxic lesion? Mutagenesis 10; 79-85