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(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Dearn et al.

Application No.: 10/854959

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For: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

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Commissioner for Patents
P.O. Box 1450
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Declaration Under 37 C.F.R. § 1.132 of Dr. Ed Cahill

Sir:

I, Dr. Ed Cahill, of 24 Adey Road, Lymm, Cheshire WA139QX, United Kingdom, hereby declare as follows:

1. I am a Manager of Product Development for AstraZeneca.

2. I have ten years of experience in the pharmaceutical industry developing both liquid and solid dosage forms. I have a Bachelor of Science Degree in Combined Science (Biochemistry) from the Polythenic of North London, an MSc degree in Toxicology from the University of Surrey, U.K., and a Ph.D. degree in the Pharmaceutical Sciences from the University of Nottingham, U.K. In addition, I was a visiting lecturer from at John Moores University in Liverpool, U.K. and have authored six peer-reviewed scientific articles.

3. Experiments were performed under my direction (depicted as **Exhibit A** attached hereto), to compare the stability of zolmitriptan at different pHs using citric acid buffers.

4. These experiments indicate that the amount of zolmitriptan degradation products upon prolonged storage was significantly less at a pH below 6, for example at pH 5.0 and 3.0, as compared to pH 7.4 or to pH 7.0.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code and that willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Ed Cahill

Dated: 11 Nov 2005 Signature: E. Cahill

Exhibit A

Stability studies of zolmitriptan at different pHs using citric acid buffers have been performed by AstraZeneca to show that intranasal formulations of zolmitriptan are significantly more the chemically storage stable below pH 7, particularly below pH 6.0. The formulations were prepared by dissolving zolmitriptan in a solution of citric acid, adding sufficient of a solution of disodium phosphate to give the required pH and diluting to the required volume with water. The formulations and study conditions are described in the sections below.

STUDY 1

In Study 1, solutions with a nominal zolmitriptan concentration of 25 mg/ml (2.5mg/ dose) were prepared at pH 3.0, pH 5.0 and pH 7.4. These solutions were tested for levels of degradation products after storage at 50°C for 8 weeks in darkness.

Study 1 Formulation compositions

	pH 3.0	pH 5.0	pH 7.4
Zolmitriptan	2.5 mg	2.5 mg	2.5 mg
Citric Acid (anhydrous)	3.2 mg	1.3 mg	0.6 mg
Disodium Phosphate (dodecahydrate) 0.2M	q.s. to pH 3.0	q.s. to pH 5.0	q.s. to pH 7.4
Water for injection	to 1ml	to 1ml	to 1ml

The results of the degradation products analysis are given in the following table:

Study 1: Results for the Degradation Products after storage at 50°C for 8 weeks.

	Degradation Products (% w/w)
pH 3	2.5
pH 5	2.4
pH 7.4	7.4

STUDIES 2 and 3

In Studies 2 and 3, solutions with a nominal zolmitriptan concentration of 50 mg/ml (5mg/ dose) were prepared at pH 3, pH 5 and pH 7. These solutions were tested for degradation products after storage at 50°C for 8 weeks in darkness (Study 2) and 25°C for 26 weeks in darkness (Study 3), respectively.

Studies 2 and 3 Formulation Compositions

	pH3.0	pH5.0	pH 7.0
Zolmitriptan	5 mg	5 mg	5 mg

Citric Acid (anhydrous)	8.7 mg	2.6 mg	1.6 mg
Disodium Phosphate (dodecahydrate) 0.2M	q.s to pH 3.0	q.s to pH 5.0	q.s to pH 7.0
Water for injection	to 1 ml	to 1 ml	to 1 ml

The results of the degradation products analysis at each of the two conditions are given in the following tables:

Study 2: Results for the Degradation Products after storage at 50°C for 8 weeks.

	Degradation Products (% w/w)
pH 3.0	1.9
pH 5.0	2.1
pH 7.0	3.6

Study 3: Results for the Degradation Products after storage at 25°C for 26 weeks.

	Degradation Products (% w/w)
pH 3.0	1.8
pH 5.0	1.0
pH 7.0	5.0

Method of Analysis:
HPLC was used to measure the degradation products in Study 1 and 2. A 15 cm x 5 mm Spherisorb S3ODS-2 column operating at a temperature of 40°C with an eluant consisting of 1730 part Water, 270 parts Acetonitrile, 2 parts Trifluoroacetic acid and 0.5 part Triethylamine was used at a flow rate of 1.6 ml/min. Detection was by UV at a wavelength of 210 nm.

The improved chemical storage stability achieved by the present invention is evident from a comparison of the data in Studies 1, 2 and 3. Study 1 clearly shows that after 8 weeks at 50°C in darkness 7.4% degradation products were measured in the zolmitriptan formulation when the pH was 7.4 while at pH 5.0 and 3.0, respectively, the degradation products were only 2.4 and 2.5, respectively. Using twice the amount of zolmitriptan in the Study 2 formulation and preparing the study under the same conditions as Study 1 with regard to time, temperature and darkness, the degradation products obtained were 3.6% at pH 7.0, 2.1 % at pH 5.0 and 1.9% at pH 3.0. Using an identical zolmitriptan formulation in Study 3 as in Study 2 but storage at 25°C in darkness for 26 weeks, the obtained degradation products were 5.0 at pH 7.0, 1.0 at pH 5.0 and 1.8 at pH 3.0. These studies clearly show the amount of storage degradation products were significantly less at pH below 6, specifically at pH 5.0 and 3.0 compared to pH 7.4 and 7.0.