

TRANSDERMAL NICOTINE PATCHES

IS THE STOWIC PATCH A SIGNIFICANT TECHNICAL ADVANCE AND IS IT LIKELY TO BE DEVELOPED INTO A SALABLE PRODUCT FOR MASS MARKETS?

The technology for transdermal administration of ethical pharmaceuticals has been in use for over ten years. Transdermal nicotine patches (TNP's), which are marketed as a major advance in smoking cessation therapy, are a refinement of this technology. They were first introduced in Europe in 1990 and were introduced in the US in late 1991. In the US, they are available only by prescription; however, in Ireland and Italy, they are available as over-the-counter (OTC) products. TNP's are now available in thirty-seven countries.

In the U.S., TNP's are marketed specifically as an aid for smoking cessation along with significant patient support programs that include access to trained smoking cessation specialists via a toll-free hotline, referrals to smoking cessation clinics, educational materials for families of smokers, and audio tapes. Likewise there is substantial promotional activities for physicians and pharmacists including sample kits and educational materials. There are also joint programs with the American Medical Association and the American Lung Association.

The three major firms in the US market are Ciba-Geigy (Habitrol brand), Marion Merrell Dow (Nicoderm brand, technology licensed from Alza), and Lederle Laboratories division of American Cyanamid (Prostep brand, technology licensed from Elan). A fourth firm, Warner-Lambert, is expected to launch its Nicotrol brand (technology licensed from Cygnus/Kabi Pharmacia), once FDA approval is granted later this year.

The Stowic patch may represent an advance over other TNP's based upon its claimed ability to deliver nicotine at a constant rate that is independent of its concentration in the patch. It would appear that it could be developed on a mass market basis.

DOES THE PATCH (TNP) REPRESENT A SIGNIFICANT THREAT TO THE TOBACCO INDUSTRY?

These products appear to represent a potential significant threat to the tobacco industry. Early volume indications are very concerning, however, the extent of the threat will depend upon the degree of the patch's success in enhancing long term cigarette abstinence and safe usage. The impact on industry cigarette sales in the short term will not be significant, but the cumulative impact could have a major effect on cigarette volumes if early acceptance patterns of the patches continue. The threat will increase if these products are granted over-the-counter distribution rights in major markets.

Analyst sales estimates continue to be surpassed. In the U.S. market, there have been numerous reports of supply shortages. Estimated first quarter sales were reportedly in excess of \$200 million (Habitrol, \$150 million; Nicoderm, \$50 million; and Prostep, \$15 million). Analysts estimates from earlier this year projected sales for the year 2000, to be \$2 billion, based on much lower expectations for 1992 sales. This should be compared to the sales of Nicorette gum, which was introduced in 1984, and had 1991 sales of only \$129 million. An additional threat could arise if a related product is marketed by the pharmaceutical companies as an alternative to smoking, leveraging on the beneficial properties of nicotine. Such threat would grow dramatically if the product would become available on an over-the-counter basis.

In terms of product characteristics, the dosage forms are typically 10, 20 or 30 mg delivered nicotine per patch. Absorption is slow and continuous. Peak blood levels are attained after about 2 hours following application (see attachment A). Blood nicotine levels are maintained at a range of 17 to 24 ng/mL.

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The average 24-hour blood nicotine concentrations resulting from use of a 21 mg patch are somewhat lower but comparable to smoking a pack of cigarettes. The pattern of the blood nicotine concentrations attained by smoking vs. the patch, however, is different. With smoking, blood nicotine absorption is very rapid. Blood nicotine concentrations go through a series of peaks and troughs with successive cigarette smoking throughout the day (see attachments B-1, B-2, B-3). With the patch, nicotine absorption is relatively slow and continuous and peak blood levels are not as high as with cigarette smoking.

Skin irritation appears to be a persistent problem associated with use of the patch for greater than 4 weeks. This could be a limiting factor in the prolonged use of the skin patch, however, skin irritation can be overcome by rotation of the site of patch application and it is likely that product improvements will be directed at this issue.

Based on clinical trials of the nicotine patch, short term smoking cessation rates are generally twice the success rates of placebo groups. Longer term (one year) abstinence rates drop substantially and range from 15% to 35% which are comparable to those of traditional behavioral modification therapies. Its long-term success rate as a smoking cessation device therefore remains to be determined.

WHAT SHOULD BE THE REACTION, IF ANY, BY B.A.T INDUSTRIES?

The pharmaceutical companies will undoubtedly seek over-the-counter status for the TNP's very aggressively. We have received reports of this strategic focus along with indications that other forms of nicotine delivery are being developed.

We should closely monitor all technical and marketing developments related to the skin patch and other nicotine delivery systems such as the nasal spray and the vapor inhaler.

We need to carefully consider the product liability and regulatory issues associated with any B.A.T involvement in nicotine delivery systems before extensive further business analyses take place.

Increasing smoking restrictions will expand the market for an alternative to cigarettes at work, on airplanes, etc. The broad area of non-ignitable, tobacco-based products represents a potential major business opportunity for the Group. While the number of different forms such products might take is quite large, a capsule, lozenge or mint-type product appears most promising at this time. The attributes required to make such a decision viable are:

- Legal and social acceptability
- Good product taste/attribute delivery
- An acceptable business and product image
- Potential tie-in with current brand names
- Distribution channels similar to the cigarette business
- Retail placement in cigarette section

While there are a number of hurdles to overcome, we believe these types of opportunities should be explored aggressively as the marketplace changes.

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ATTACHMENT A

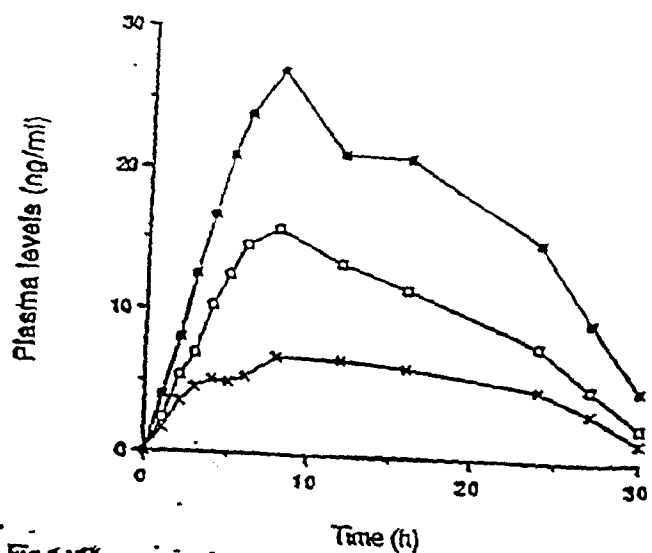


Fig. 1. Plasma nicotine levels following 24 h single application of × 15 mg, □ 30 mg and ■ 60 mg transdermal patches

SOURCE: BARRON, ET.AL., 1989

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ATTACHMENT B-1

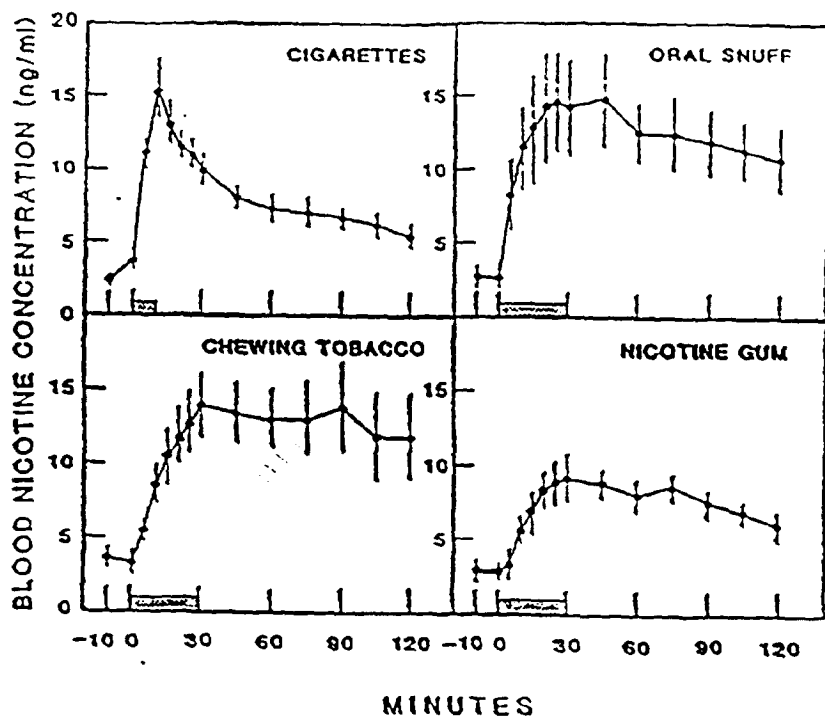
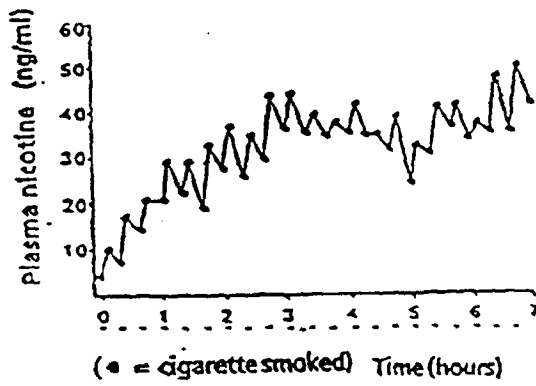


Fig. 1. Blood nicotine concentrations during and after cigarette smoking, oral snuff, chewing tobacco, and nicotine gum (two 2 mg pieces). Data represent average values for 10 subjects; vertical bars indicate SE. Shaded bars above time axis indicate period of tobacco or nicotine gum exposure.

SOURCE: BENOWITZ, ET.AL., 1988

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ATTACHMENT B-2

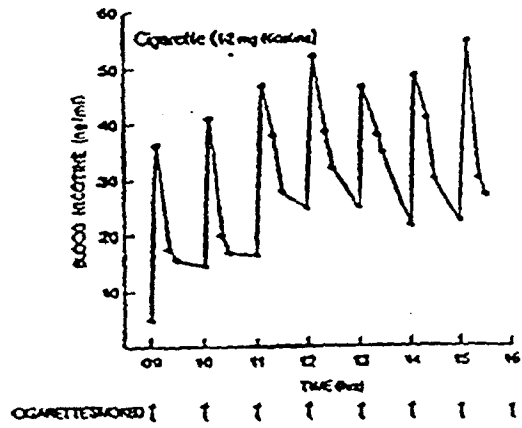


3. Blood nicotine levels of a heavy smoker, smoking three cigarettes an hour. From Russell & Feyerabend (1978).

SOURCE: RUSSELL ET AL., 1987

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ATTACHMENT B-3



1. 2. Blood nicotine levels of an inhaling smoker, smoking one cigarette an hour. From Russell et al. (1976).

SOURCE: RUSSELL ET AL., 1987

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