

Assessment of Sensitizing Potential

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2060 Cernitin T60

2065 Cernitin GBX

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INTRODUCTION

A combination of 2060 CERNITIN T 60 and 2065 CERNITIN GBX was found to be sensitizing in guinea pigs when tested according to the maximization method of Magnusson and Kligman (1). In this test, a 5% suspension of CERNITIN T 60 and CERNITIN GBX (60 + 3) was administered intracutaneously together with complete Freund adjuvant, followed after 7 days by an epidermal application of a 25% suspension of the test substance combination. Two weeks after the induction exposure, the animals were challenged by a further topical application of the same suspension. They revealed a positive reaction.

Thus, the maximization procedure demonstrated an allergenic potential or sensitizing capacity of the test material, without however indicating an actual risk of sensitization in man.

In order to interpret the experimental finding it is important to realize that the guinea pig maximization test is a diagnostic procedure for predicting delayed-type sensitivity to proteins and soluble antigen-antibody complexes on the skin. The cell-mediated reaction produces contact dermatitis and other allergies of the tuberculin-type. However, allergens associated with pollens induce immediate-type reactions which are associated

with circulating antibodies of the IgE class. Allergens of this sort are capable of inducing hay fever, bronchial asthma, urticaria, and anaphylactic shock.

It is to be expected that water soluble protein or peptide components of CERNITIN T 60 may induce a delayed type reaction when injected intradermally with complete Freund adjuvant as immune enhancer. The relevance of the laboratory procedure as it was performed is however limited as it does not apply to the practical use conditions of the CERNITIN extracts of pollens. Since the therapeutic use is oral rather than topical, it is more appropriate to rely on information of occupational exposure and of side effects in patients in order to assess the risk of allergic reactions. Atopic patients may be considered to be at particular risk of developing allergic disorders. Such individuals were subjected to immunotherapy with high doses of CERNILTON in order to achieve desensitization upon oral treatment.

MEDICAL ASSESSMENT

Occupational Exposure

No symptoms suggestive of pollen allergies have been reported over 5 years in personnel engaged in production of the pollen extracts CERNITIN T 60 and GBX (2).

Adverse Effects During Therapy of Benign Prostatic Hyperplasia

Controlled clinical studies confirmed the good tolerability of CERNILTON N. In a study conducted over 24 weeks, 3 patients out of 92 treated reported gastrointestinal side effects (3). A similar incidence (4%) occurred in an open study which involved 1798 patients treated for 24 weeks (2 tablets 100 mg t.i.d.) (4).

During 1984-1991 (sales volume 145'801'000 tablets CERNILTON/CERNILTON N), post-marketing surveillance in Germany resulted in 113 reports of adverse effects. The large majority (96 cases) consisted of gastrointestinal disturbances, 10 developed a variety of cutaneous symptoms and only 2 developed "allergy" of a non-specified nature (5).

By contrast, no reports on side effects of CERNILTON/ADRENOPROSTAL were received in Switzerland (6), or in Korea of CERNILTON tablets sold since 1975 (7), or in Japan where CERNILTON is marketed since 1969 (8). Likewise, no side effects are reported in Argentina (sales volume > 150 million CERNILTON tablets since 1975) (9), or in Austria (> 8 000'000 CERNILTON/PROSTAFLOL tablets sold since 1983) (10).

Tolerance Study in Patients with Pollen Allergy

Twenty eight patients (18 men and 10 women) suffering from seasonal allergic rhinitis (pollinosis) received 4 daily capsules of STHENOREX (120 mg T60 and 6 mg GBX per capsule) at intervals, including the pollen season. Although the skin test to STHENOREX was positive, no reaction to oral treatment was observed and there was no improvement of the allergic condition. (11).

Immunotherapy

In an open study in Switzerland, 44 patients suffering from seasonal allergic rhinitis were treated for 2 months with daily doses of 840 mg T60 and 42 mg GBX (one FH 84 sachet), or 1680 mg T60 and 84 mg GBX (2 sachets), respectively. This amount is equal to 4.5 to 9 times the usual daily dose of CERNILTON. Apart that the treatment was considered effective in 70% of the patients, there were no untoward allergic reactions, or other side effects (12).

A similar study was carried out in Argentina on a total of 47 patients who received one or two sachets of FH 84, or placebo. Apart from one patient each who experienced transient diarrhea or

sinusitis, treatment was uneventful (therapeutic effects due to FH 84 could not be ascertained as other drugs with antiallergic properties were administered) (12).

A double-blind, placebo controlled study was performed in Italy (13). Thirty four pollinosis patients received 2 sachets of FH 84 for 30 days, and 41 matching patients the placebo only. There was no overall significant effect of treatment and no side effects were encountered.

CONCLUSION

The vast clinical experience indicates that CERNITIN T 60 and CERNITIN GBX are well tolerated. Side effects are rare and generally limited to the gastrointestinal tract. Reactions reminiscent of allergic effects have been reported in single cases only.

It is concluded that the standardized CERNITIN extract of pollen is devoid of allergenic properties when administered by the oral route. This has amply been demonstrated in therapeutic use as well as in special studies involving high dosage in atopic patients.

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