PHARMACO-TOXICOLOGICAL REPORT

ON AXSAIN CREAM (Capsaicin 0.075%)

by

CONTENTS

PRODUCT PROFILE - AXSAIN CREAM 0.075%

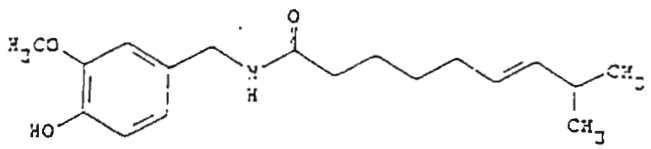
A. TYPE OF APPLICATION

This is a medically targeted, abridged product licence application for marketing authorisation in the United Kingdom for Axsain Cream 0.075% under PL 10670/10. This application cross-refers to an existing product licence held by Euroderma Ltd for Axsain Cream 0.075% PL10670/0003, which is indicated in the management of post-herpetic neuralgia and was approved on 20/8/1992.

Axsain Cream contains 0.075% capsaicin, a naturally occurring substance found in capsicum fruit.

B. CHEMICAL AND PHARMACOKINETIC PROPERTIES

Capsaicin, chemical name trans-8-methyl-N-vanillyl-6-nonenamide, is an alkaloid with the following structure:



Capsaicin has a molecular weight of 305.40 and forms white translucent crystals which melt at 64.5°C.

Absorption after topical application is unknown. Average consumption of dietary spice from capsicum fruit has been estimated as 2.5g/person/day in India and 5.0g/person/day in Thailand. Capsaicin content in capsicum fruit is approximately 1%, therefore daily dietary intake of capsaicin may range from 0.5-1mg/kg/day for a 50kg person. Application of two tubes of Axsain cream 0.075% (90g) each week results in a 9.6mg/day topical exposure. Assuming 100% absorption in a 50kg person, daily exposure would be 0.192mg/kg, which is approximately one-third to one-quarter of the above-mentioned dietary intake.

C. INDICATIONS

Axsain Cream 0.075% is indicated for the symptomatic management of painful diabetic peripheral polyneuropathy.

Although the precise mechanism of action of capsaicin is not fully understood, evidence suggests that capsaicin renders skin insensitive to pain by depleting and preventing subsequent reaccumulation of Substance P in peripheral sensory neurons. Substance P is one of the principal chemomediators of pain impulses from the periphery to the central nervous system and also plays a role in inducing inflammatory response.

Adults and elderly should apply Axsain Cream 0.075% to the affected area not more than 3 to 4 times daily. Axsain is not suitable for use in children.

D. PRECAUTIONS

Axsain Cream 0.075% is contra-indicated on broken skin or irritated skin. It should be kept away from the eyes. After applying Axsain cream with the fingers, hands should be washed immediately.

Axsain may cause transient burning on application. This burning is observed more frequently when application schedules of less than 3 to 4 times daily are utilised.

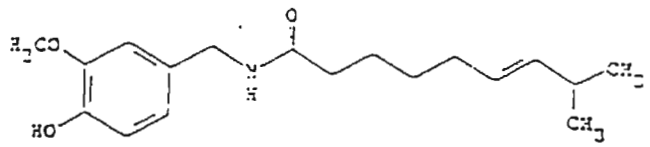
E. MARKETING/POST-MARKETING

Axsain Cream 0.075% is licensed for the symptomatic relief of pain associated with post-herpetic neuralgia in the UK, and is approved for symptomatic management of painful diabetic peripheral polyneuropathy in the US, Canada, Australia and Eire.

1. INTRODUCTION

Capsaicin is an alkaloid, with a highly pungent taste but little odour, which occurs in the fruits of various species of the capsicum plant. Capsicum fruits (chilli peppers) have been widely used, as a spice in food preparation, for many hundreds of years and its use for this purpose in western societies is increasing as one-time regional foods become more global in distribution.

Capsaicin (trans-8-methyl-N-vanillyl-6-noneamide) is present in capsicum fruits in varying amounts ranging from 0.1 to 1.0% and likewise extracts of capsicum oleoresin, contain varying quantities of capsaicin. When purified, capsaicin occurs as white translucent crystals with a melting point of 64.5°C; it has the following structural formula:



Capsaicin (molecular weight: 305.40)

Preparations containing capsaicin, usually crude extracts of the whole fruit, have been used for many years for direct application to the skin to relieve local pain. The FDA panel which reviewed OTC capsicum-containing preparations for local application considered that the beneficial effects of these preparations were due to a "counter-irritant" effect involving stimulation of cutaneous sensory receptors producing a feeling of local warmth. However, it was noted that capsaicin differed from other local irritants in that it produced practically no reddening of the skin despite the subjective feeling of warmth. The panel concluded that products containing 0.025 to 0.25% capsaicin are effective for use as OTC analgesics (FDA, 1979).

In recent years, capsaicin has been widely used as a tool in neuropharmacological research following a number of reports which suggest that it has selective effects on the transmission of painful stimuli in sensory nerves and thus clearly differs from traditional counter-irritants such as camphor and mustard oil. AXSAIN CREAM, containing 0.075% capsaicin as active ingredient, has been approved for clinical use in the symptomatic relief of post-herpetic neuralgia in the USA, Ireland and the UK. The current application relates to AXSAIN CREAM 0.075% intended for the symptomatic management of painful diabetic peripheral polyneuropathy. AXSAIN CREAM has been approved for this indication in the USA and Ireland.

2. COMPONENTS OF AXSAIN CREAM

AXSAIN CREAM contains the following components:

Capsaicin	0.075%
Cetyl alcohol Ph.Eur	[redacted]
Isopropyl myristate Ph.Eur	
White soft paraffin BP	
Benzyl alcohol Ph.Eur	
Glyceryl stearate and PEG100 stearate (Arlacel 165)	
Sorbitol solution Ph.Eur	
Purified water Ph.Eur	

* For ease of handling, capsaicin is supplied as a capsaicin/cetyl alcohol premix, since capsaicin active substance is an irritant material. The actual quantity of cetyl alcohol used depends on the purity of capsaicin as determined by HPLC.

Of the components of AXSAIN CREAM, only capsaicin is considered to have any pharmaco-toxicological activity when applied externally to intact skin, the remaining components are all present as excipients and are not considered to pose any significant toxicological hazard to man when used externally. This report will deal only with the potential pharmaco-toxicological activity of capsaicin when applied to intact skin.

3. PHARMACOLOGY

3.1. Effects related to the therapeutic activity of capsaicin

3.1.1. Effects of capsaicin on sensory nerves:

Hogyes (1878) was the first to suggest that the pungent and irritant effects of extracts of capsicum are mediated predominantly via sensory nerves. However, it was more than 80 years later before it was realized that capsaicin, the active principle of capsicum, also exerts a long-term sensory receptor blocking action which is valuable in the functional investigation of afferent neurons (Jancso, 1960). It is this action to cause a functional block in sensory nerves which is the basis of the local analgesic effect of capsaicin-containing preparations such as AXSAIN CREAM.

Holzer (1991) has extensively reviewed the effects of capsaicin on sensory nerves and has described two main pharmacological actions for it:

(a) An action selective for thin afferent neurons consisting of an initial short-lasting stimulation that can be followed by desensitization to capsaicin itself and to other stimuli of sensory nerves. Both of these actions appear to arise from a common mechanism of action involving activation of a cation channel in the cell membrane of sensory nerves.

(b) A non-selective effect manifesting itself as a transient depression of excitability with no long-lasting consequences for the cell.

It is likely that the local analgesic effects of capsaicin-containing preparations, such as AXSAIN CREAM, are related only to the first type of action since the non-selective effects of capsaicin are only evident at concentrations of capsaicin orders of magnitude higher than those needed to first stimulate and then block sensory nerves.

3.1.2. Capsaicin-sensitive afferent neurons:

It is difficult to define precisely capsaicin-sensitive afferent neurons, since they do not completely overlap with any single population of afferent neurons that have been classified according to morphological, neurochemical or functional criteria (Holzer, 1991). The majority of capsaicin-sensitive neurons have small to medium-sized cell bodies that are connected to unmyelinated (C) or thinly myelinated (Aδ) nerve fibres (Lawson & Harper, 1984). However, not all unmyelinated afferent neurons conducting in the C and Aδ fibre range are sensitive to capsaicin (Holzer, 1991).

The mechanisms involved in the transmission processes in afferent sensory neurons are poorly understood compared with the well-defined mechanisms which have been elucidated in efferent motor and autonomic neurons. However, a number of peptides are present in afferent neurons which have been suggested as possible candidates for neurotransmitter or mediator roles. Among these peptides, the most widely regarded to be a likely neuro-transmitter is Substance P and there is compelling evidence to suggest that capsaicin may exert its inhibitory actions on sensory neurons via an action on this substance. Thus, capsaicin applied locally to the rat sciatic nerve blocked axoplasmic transport of both Substance P and somatostatin but did not affect the neuronal transport of either noradrenaline or acetylcholinesterase. Similar inhibition of neuronal transport of Substance P was also demonstrated in sciatic nerves of guinea-pig, cat and rabbit (Gamse *et al.*, 1982). These workers also showed that local application of capsaicin to sciatic nerve resulted in a decrease in the neuronal content of Substance P in skin and in sciatic nerve distal to the site of application and also in the dorsal root ganglia, dorsal roots and the dorsal half of the spinal cord segments L4-5. This depletion of Substance P was associated with an early loss of response to noxious stimuli (hot plate test) and was closely paralleled by a reduction in plasma extravasation induced by mustard oil on the skin of the hind-paw. It was concluded that capsaicin, applied to peripheral nerve, inhibits axoplasmic transport in sensory nerves resulting in long-term biochemical and functional changes of the entire sensory neuron.

Although capsaicin-sensitive afferent neurons are heterogeneous in terms of their sensory modality and the functions they subserve, the most consistent functional change associated with the neurotoxic effect of capsaicin is a long-term inhibition of chemi-nociception (Szolcsanyi, 1984).

3.1.3. Capsaicin-insensitive neurons:

Some afferent neurons, with thickly myelinated axons, conducting in the Aα and Aβ range are first stimulated and blocked transiently by acute administration of capsaicin but are very insensitive to the long-term neurotoxic action of the drug (Holzer, 1991). Capsaicin has been shown to have no effects, either stimulatory or inhibitory, on either efferent motor neurons or on efferent neurons of the autonomic nervous system (Szolcsanyi *et al.*, 1975).

3.1.4. Cell non-selective actions of capsaicin:

In addition to its actions on sensory neurons, capsaicin also exerts cell non-selective effects on a variety of excitable cells. In contrast to the effects on sensory neurons, these non-selective effects do not seem to be mediated via a specific recognition site but may be due to physicochemical interactions of the lipophilic capsaicin molecule with the cell membrane, especially when high concentrations of the drug are used (Holzer, 1991). Unlike the sensory neuron effects of capsaicin, the non-selective effects do not show either desensitization or neurotoxicity.

3.2. General pharmacological activity of capsaicin

Relatively few studies have been published on the general pharmacological activity of capsaicin and those which have been located have used parenteral bolus administration of the drug and thus are of only marginal relevance to preparations applied to the skin.

3.2.1. Effects on the cardiovascular and respiratory systems:

Bevan (1962) injected capsaicin (20 µg/kg) into the pulmonary arterial tree of the cat and observed no significant difference between the reflex hypotensive effects seen when the injection was made into the right or left pulmonary arteries both distal to the bifurcation. The hypotensive response was almost absent when the compound was administered into the right and left pulmonary hila. Following vagotomy, the hypotensive effect of capsaicin was abolished. The results suggest that sensory afferent nerve endings stimulated by capsaicin are situated somewhere in the pulmonary artery and in the right and left branches proximal to the level of the hilus.

In anaesthetized dogs, intravenously administered capsaicin (10 to 20 mg) caused transient apnoea, bradycardia and hypotension associated with reduced blood flow in the mesenteric, renal and femoral arteries but increased flow in the carotid artery. There was a shortening of the apnoeic period and abolition of the bradycardia following vagotomy. In these experiments, cardiac contractility was depressed *in vivo* although it was increased *in vitro* in guinea-pig isolated atria. In non-anaesthetized dogs, capsaicin caused a marked increase in systemic arterial blood pressure associated with characteristic behavioural changes.

4. PHARMACOKINETICS

No studies have been performed to investigate the possible systemic absorption of capsaicin from AXSAIN CREAM; this is to some extent due to the low dose of capsaicin applied and the ensuing difficulty in establishing a suitable assay method for capsaicin in biological fluids. It is unlikely that marked systemic effects would occur resulting from transdermal absorption of capsaicin in the low concentrations present in AXSAIN CREAM.

4.1. Animal studies

In rats, following oral administration, capsaicin is absorbed in the small intestine by a non-active process which is not inhibited by either 2,4-dinitrophenol or sodium cyanide. The principal metabolic pathway for capsaicin appears to be hepatic hydroxylation of the 5 position of the ring. There is some evidence to suggest the involvement of cytochrome P450 in the metabolism of capsaicin since it prolongs phenobarbitone sleeping time and pretreatment with phenobarbitone enhances capsaicin metabolism (Anon., 1986). Other results in laboratory species suggest that after either intravenous (Saria *et al.*, 1981) or oral (Schwen, 1983) administration, capsaicin is rapidly cleared from the bloodstream with half-lives of less than 30 minutes by both routes.

5. TOXICOLOGY

5.1. Single dose studies

Sollman (1957) reported that, in fasting young rabbits, the oral administration of 28 ml of capsicum oleo-resin was associated with diarrhoea and loss of body weight followed by full recovery. However, an oral dose of 56 ml was shown to be lethal in the same species. Glinsukon *et al.* (1980) reported an oral LD_{50} value for capsaicin in mice of approximately 60-75 mg/kg and concluded from their results that neither capsaicin nor extracts of capsicum were likely to pose a toxic hazard to man when used to flavour food.

5.2. Repeat dosing studies

Monsereenusorn (1983) cited some early studies in which either capsicum or capsaicin was administered daily over varying periods to rabbits and rats. It was found that daily dosing of rabbits with either capsaicin or capsicum produced unspecified pathologic changes in several organs including kidneys and liver, and there was a reduction in the rate of growth of rats treated with capsicum (Nopanitaya, 1973). This latter observation was confirmed by Rozin *et al.* (1979) who reported that rats accepted a diet containing 1.5 to 15% capsicum fruit (equivalent to about 9 to 90 mg/kg/day capsaicin) as well as they did a normal control diet although the growth rate of the capsicum-treated rats was less than that of controls.

Monsereenusorn (1983) treated groups of 10 to 14 rats with daily oral (gavage) doses of either capsaicin (50 mg/kg/day) or capsicum crude extract (500 mg/kg/day) for periods of either 10, 20, 30, 40, 50 or 60 days. There were no deaths during the study but there was a reduction in the rate of growth of rats receiving both treatments from day 40 onwards. This effect on growth was associated with an increased food consumption in treated groups compared to controls. There was some evidence to suggest that body temperature of treated animals increased after about 30 days of treatment and it is therefore possible that the reduced rate of growth and increased food intake could be related to thermogenic effects of capsicum extracts and capsaicin. A number of clinical chemistry values, including blood urea nitrogen, glucose, phospholipids, triglycerides, total cholesterol, free fatty acids, glutamic pyruvic transaminase and alkaline phosphatase, were reduced in animals treated for more than 30 days with either test material. However, there

were no obvious correlations between any of these changes and possible treatment-related adverse effects. Haematological values and renal concentrating ability were both unaffected by either treatment and autopsy revealed few treatment-related signs apart from slight hyperaemia of the liver and reddening of the gastric mucosa in both treated groups at 60 days. Overall, this study indicated that capsaicin showed few signs of significant toxicity when administered for up to 60 days at the high level of 50 mg/kg/day (equivalent to approximately 5-10 g/kg/day of capsicum fruit).

5.3. Neurotoxicity of capsaicin

In addition to its action in causing a reversible stimulation followed by blockade of transmission in sensory afferent nerves, capsaicin has also been shown to cause a long-term, sometimes irreversible, toxic effect on some sensory nerves. This effect was first reported by Jancso *et al.* (1977) who observed that a single subcutaneous administration of capsaicin (50 mg/kg) to newborn rats caused a life-long degeneration of B-type primary afferent neurons. This degeneration takes place within 30 minutes of administration, is permanent and involves most B-type neurons and their peripheral and central nerve processes. Holzer (1991) reviewed the published data relating to capsaicin neurotoxicity and concluded that the effect is dosage-related with a threshold dose in rats of about 5 to 15 mg/kg and a maximal effect occurring at 50 mg/kg. The loss of unmyelinated afferent fibres from major peripheral nerves, such as the sciatic, with the 50 mg/kg dose of capsaicin, has been estimated to be between 40 and 67%, whereas in the dorsal roots up to 95% of unmyelinated fibres were lost (see Holzer, 1991, for references). The loss of thin afferent nerve fibres is associated with degeneration of cell bodies from the spinal and sensory ganglia. The neurotoxic effect is not specific for unmyelinated fibres and at capsaicin dosage levels above 25 mg/kg there is also some loss of myelinated Aδ-fibres, whereas over the dosage range 10-25 mg/kg there was a selective loss of 95% of all unmyelinated afferents without any observable loss of myelinated fibres (Nagy *et al.*, 1983). Loss of sensory afferent fibres under the influence of capsaicin is paralleled by a depletion of biological markers associated with thin primary afferent neurones. Most notable is the reduction of both endogenous levels and synthetic capacity of Substance P. Predictably, the loss of sensory neurons in newborn rats is associated with permanent sensory and functional deficits involving both afferent and local effector functions of sensory neurons. The local effector functions include local vasodilatation and increased vascular permeability. Afferent functions impaired by neonatal capsaicin administration include warmth reception and thermoregulation, cardiovascular reflexes, visceral and neuroendocrine reflexes and changes in nociception. Changes in nociception lead to changes in nociception-associated avoidance reactions particularly those evoked by chemical stimuli.

The evidence, as reviewed by Holzer (1991), suggests that the susceptibility of rats to the neurotoxic effects of capsaicin diminish with increasing age. Thus, during the first 12 days of life, rats are very sensitive to the neurotoxic effect whereas in rats, aged 20 days or above, capsaicin generally only causes a reversible reduction in chemonociception with no concomittant neural degeneration or depletion of Substance P. However, long-term, possibly irreversible, effects may occur in adult animals treated with high dosage levels of capsaicin. Dosage levels of 35-300 mg/kg capsaicin (subcutaneously) in adult rats caused morphological abnormalities

in B-type sensory neurons but not in either A-type afferents or sympathetic efferent neurons when examined 1 to 60 days post-treatment (Chiba *et al.*, 1986).

Overall, there is a considerable body of evidence to suggest that at high dose levels, and particularly in very young animals, capsaicin may cause long-term or even permanent damage to sensory neurons. However, there appears to be a well-marked threshold dose in animals below which capsaicin does not exert this action and this dosage level is of a higher order of magnitude than the maximum dose likely to be absorbed transdermally from AXSAIN CREAM when used in humans. The lack of a neurotoxic effect for capsaicin, when applied long-term to the skin of rats, has been confirmed by McMahon *et al.* (1991).

5.4. Reproduction studies

No formal animal reproduction studies have been performed with AXSAIN CREAM and no literature reports have been located which relate to possible effects of either capsicum or capsaicin on reproductive function.

5.5. Genotoxicity tests

The available published reports relating to the genotoxic potential of capsaicin have produced conflicting data with both positive and negative responses reported in the Ames bacterial reversion test and in V79 Chinese hamster ovary cells *in vitro*. In the only located *in vivo* test, capsaicin produced a positive response in a micronucleus test at a dose level close to the LD_{50} value.

Buchanan *et al.* (1981) found no evidence for a mutagenic effect of capsaicin in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1538 either in the presence or absence of metabolic activation with rat liver S-9 mixture. Subsequently, Toth *et al* (1984) reported negative effects with capsaicin in *S.typhimurium* strains TA97, TA100 and TA102 both in the absence and presence of mouse liver S-9 mixture. However, in the presence of rat liver S-9 mix there was a dose-dependent increase in revertant numbers in strain TA98 at dosage levels of capsaicin up to 750 µg/plate. This positive result with strain TA98 could not be repeated by the same authors using identical experimental conditions (unpublished observations cited by Toth & Gannett, 1992). Positive results in the Ames test using various strains of *S.typhimurium* were reported by Nagabhushan & Bhide (1985) with both chilli extract and capsaicin in the presence of metabolic activation. Nagabhushan & Bhide (1985) also found that both chilli extract and capsaicin were non-mutagenic when tested in V79 Chinese hamster ovary cells using the 8-azoguananine-resistant assay whereas, using the same test system, Lawson & Gannett (1989) reported positive effects for both capsaicin and dihydrocapsaicin.

In the only *in vivo* test report which has been located, Nagabhushan & Bhide (1985) reported that capsaicin produced a positive response in the micronucleus test at a dose level close to the LD_{50} value.

5.6. Carcinogenicity tests

Conflicting data have also been reported in the literature relating to the potential carcinogenicity of capsicum extracts and of capsaicin. Toth *et al.* (1984) treated groups of 8 (4 of each sex) Swiss albino mice with capsaicin admixed with the diet at concentrations of 0.0625, 0.125, 0.25, 0.5 or 1.0% for 35 consecutive days. This dosage regimen resulted in mean daily intakes of capsaicin ranging from 2 to 30 mg/mouse. Following the end of treatment, the mice were observed until they died or became moribund. Capsaicin treatment had no effect on survival rates compared to controls fed normal diet. Post mortem examinations revealed that a single animal in each treated group (apart from that receiving 1% capsaicin) developed an adenocarcinoma of the duodenum between weeks 72 and 126. Watts (1985), in reviewing this test, concluded that in the absence of a possible mechanism for the induction of duodenal ulcers and given the small group sizes and the well-known irritant nature of capsaicin, the results of this study provided no basis for assessing the risk to man of low doses of capsaicin. In a later study (Toth & Gannett, 1992) groups of 100 (50 of each sex) Swiss mice were treated, beginning at 6 weeks of age, for their remaining life-span with dietary capsaicin at a level of 0.03125%. The life-span of treated mice was no different from that of controls but, at terminal autopsy examination, 11 females (22%) and 7 males (14%) from the treated group had benign polypoid adenomas of the caecum compared with only 4 of each sex (8%) in the controls receiving normal diet. The difference in incidence of caecal tumours in this test only attained statistical significance for the females. The studies of Toth and his group do not provide clear-cut evidence for a carcinogenic effect of capsaicin since the tumour type showing an apparent increase in capsaicin-treated mice was different in the two studies and, as only a single dose level was used in the larger study, there was no evidence for a dosage-related effect. Other published data using capsicum extracts or capsaicin are equally inconclusive. Thus, in the early studies of Hoch-Ligetti (1951; 1952) the feeding of chilli pepper to rats was associated with an increased incidence of tumours although this observation did not lead the author to classify chilli powder as a carcinogen. Agrawal *et al.* (1986) reported that extracts of chilli peppers exhibited tumour-promoting effects in stomach and liver of mice initiated by methylacetoxy methylnitrosamine and benzene hexachloride, whereas the development of lung tumours induced by polycyclic aromatic hydrocarbons was inhibited by capsaicin (Juan-June *et al.*, 1989). A potential anti-tumour effect of capsaicin is also suggested by the work of Modly *et al.* (1986) who reported that capsaicin was a potent *in vitro* inhibitor of both human and murine epidermal metabolism of benzo(a)pyrene (BP) and of the enzyme-mediated binding of BP metabolites to DNA.

Overall, although definitive studies are lacking, the available data do not suggest that capsaicin, in the small quantities present in AXSAIN CREAM, is likely to pose a significant carcinogenic hazard to humans.

6. DISCUSSION

Although capsicum-containing preparations have long been used for the relief of local pain, it is only in recent years that evidence has accumulated which suggests that capsaicin, the active principle of capsicum fruit, has a selective action in blocking the transmission of impulses in afferent sensory neurons associated with pain perception. Numerous studies have indicated that this effect of capsaicin is

clearly distinguishable from the effects of traditional counter-irritants such as camphor and mustard oil.

The physiological mechanisms involved in the transmission of nerve impulses in sensory nerves are relatively poorly understood compared with the mass of detail available relating to transmission processes in both efferent motor and autonomic neurons. However, there is a growing body of experimental evidence which implicates Substance P as a putative neuro-transmitter or mediator in sensory neurons. Furthermore, it appears likely, from the results of a number of studies, that the action of capsaicin on transmission in sensory neurons is mediated via an inhibition of synthesis, transport and/or release of Substance P from these neurons. The action of capsaicin is not specific for a single population of sensory neurons although it is clearly selective, particularly at low dosage levels, for thin unmyelinated afferents (C-fibres). The effects of capsaicin on these fibres appear to be mediated via a specific cation channel in the cell membrane and are characterized by a brief stimulant effect followed by a more prolonged period of "desensitization" during which the neuron is insensitive to further stimulation from either capsaicin or other stimuli.

In addition to its reversible blocking action on sensory neurons, capsaicin also has a neuro-toxic action which has been demonstrated in animal studies but has not been reported in man. Neurotoxicity to capsaicin has been most clearly demonstrated in rats during the first 12 days of life, during which time a single dose of capsaicin (50 mg/kg) causes an almost total morphological and functional loss of unmyelinated C fibres. At age 20 days or more, rats are much less sensitive to the neurotoxic effect of capsaicin although there is evidence that irreversible neuronal damage may occur at high dosage levels. In very young rats, the threshold dose of capsaicin, above which neurotoxicity may occur, is about 15 mg/kg whilst in more mature animals it is at least 35 mg/kg. Neurotoxicity has not been reported following long-term application of capsaicin-containing preparations in either animal or human studies. AXSAIN CREAM contains 0.075% capsaicin which is equivalent to 7.5 mg in a 30 gram tube. If it is assumed, in an extreme case, that a whole tube of the preparation was applied to the skin and that absorption of capsaicin was complete, then the maximum dose of capsaicin would still be less than 0.2 mg/kg in a 50 kg adult or about 0.5 mg/kg in a child. These maximum doses, which are probably exaggerated by a factor of at least 10, are still well below dose levels likely to cause neurotoxicity in humans. The possibility of young children, like young rats, being more sensitive to the potential neurotoxic effects of capsaicin is guarded against by the direction in the data sheet that the preparation should not be used in children.

The available animal toxicity data relating to capsicum, capsicum extracts and capsaicin do not suggest that, in usual doses, they pose any significant toxicity hazard to man. Thus, in both single and repeat dosing studies which have been reported, capsicum extracts and capsaicin are generally well tolerated at many times even the highest estimated human intakes. Srinivasan *et al.* (1980) has estimated the human average daily intake of capsicum fruit in Thailand to be about 5 g per day, which, assuming an average capsaicin content of 0.5%, would amount to a daily dose of capsaicin of about 0.5 mg/kg/day. This dose level is likely to be significantly higher than the maximum amount which would be expected to be absorbed from AXSAIN CREAM or from other topical preparations containing even

lower amounts of capsaicin. Although no published data have been located relating to any possible effects of capsaicin on reproductive function, there is no reason to suspect, from either animal or human studies presently available, that any adverse effects in humans are likely. Genotoxicity tests using both crude extracts of capsicum and capsaicin have produced conflicting data, in one instance within a single laboratory, and overall, do not suggest that capsaicin possesses a biologically-significant level of genotoxicity. The carcinogenicity data which have been published are very difficult to evaluate because of flaws in the experimental design and have likewise produced conflicting data. The conclusion which can be drawn from these studies is that, at the present time, there is no convincing evidence for a carcinogenic action of capsaicin. It would therefore appear to be most unlikely that capsaicin, in the quantities likely to be absorbed transdermally from AXSAIN CREAM, will pose any significant carcinogenic hazard to humans.

The likely good tolerance of AXSAIN CREAM in man is supported by the data on distribution of topical capsicum-containing preparations in the U.S.A. reviewed by the OTC Panel of the FDA (FDA, 1979). They reported that one capsicum-containing product had sold more than 38.5 million units and another 22.3 million units during the period 1960 to 1972 whilst another product had annual sales of more than 0.5 million units. The manufacturers of these products reported a total of only 16 customer complaints for the year 1972 with none of these deemed to be of a serious nature. The Panel concluded that capsicum-containing preparations are safe and effective for use as external analgesics when used in preparations containing 0.025 to 0.25% capsaicin and when applied not more than 4 times daily.

The animal data reviewed in this report support the conclusions of the OTC Panel of the FDA outlined previously and I therefore conclude that AXSAIN CREAM containing 0.075% capsaicin is likely to be a safe and effective local analgesic when used according to the directions described in the data sheet.

May 1994

[redacted]

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