

# Xepin

5% w/w Cream  
(doxepin hydrochloride)

**The only clinically proven  
topical Antihistaminic Agent<sup>1</sup>**



Stop the itch-scratch cycle  
**at the first sign of a flare up**

**CLINICAL INFORMATION**  
FOR HEALTHCARE PROFESSIONALS

## Xepin 5% w/w Cream (doxepin hydrochloride)



### Pruritus/Itch

Pruritus (itch) is the most common symptom in skin disease<sup>3</sup>. It can be one of the most distressing symptoms of eczema in its various forms, and can have a profound effect on quality of life for sufferers, similar to that of chronic pain<sup>4, 5, 6</sup>. Failure to combat itch may, through continual scratching, worsen the condition causing lichenification, excoriation and secondary infection. This is known as the 'Itch-Scratch Cycle'.

**Xepin Cream** has an important role in the treatment of itch associated with eczema. Through the pharmacological properties of its active ingredient, doxepin hydrochloride, a potent H<sub>1</sub> and H<sub>2</sub> antihistaminic compound, it offers the possibility to bring localised itching under control quickly. This allows earlier transition to more benign emollient maintenance therapy or the use of lower potency steroids.

### Pathophysiology of Pruritus

The cause of pruritus in eczema is unclear. Eczematous skin biopsies reveal increased density of nerve fibres and mast cells compared with normal skin<sup>7, 8</sup>. Pruritic sensations arise from stimulation of nerve endings in the dermo-epidermal junction causing impulses to transmit along unmyelinated C-fibres, releasing substance P and other neurotransmitters. In turn, impulses pass into the spinal cord and so to the brain. C-fibres often terminate in the skin close to mast cells. A range of chemical mediators have been implicated in causing the de-granulation of mast cells including serotonin, bradykinin, substance P, endo-peptidases and histamine, which is generally held to be the most important<sup>9, 10</sup>.

After its release, histamine acts on H<sub>1</sub> and H<sub>2</sub> Receptors in the skin to stimulate the sensory C-fibres, causing cutaneous vasodilation and vascular permeability. This results in pruritus, with erythema and oedema<sup>7, 11</sup>. Muscarinic receptors may also so be involved through the mediator, acetylcholine<sup>12</sup>.

The inflammatory process in eczema is complex, involving over-reaction to allergens. Immunoglobulin E causes mast cells to de-granulate, releasing a variety of pro-inflammatory cytokines and histamine. Some of these agents may play a regulatory role by lowering the threshold of itch perception<sup>13</sup> whilst histamine is thought to have a direct effect on the itch receptor<sup>7</sup>. Scratching causes physical injury to the skin damaging keratinocytes, which further release inflammatory mediators perpetuating inflammation. Superinfection of excoriated skin also maintains or worsens inflammation and consequent itching<sup>14, 15</sup>. There are thus several potential therapeutic targets available for intervention.

## Therapeutic Approaches To Pruritus

The treatment of pruritus is directed primarily at interrupting the destructive 'itch-scratch' cycle. This involves improving skin condition, reducing inflammation and stopping the itch. Dry skin is extremely common amongst patients with atopic dermatitis. Not just uncomfortable and unsightly, the skin barrier is compromised, making the patient vulnerable to skin irritants and flare-ups of their condition.

<p><b>Emollients</b> play an important role in the long-term management of eczema with a wide range available to suit patient skin.</p>	<p>Itch reduction qualities of emollients are secondary to their moisturising properties, so response to it is slow</p>
<p><b>Topical steroids</b> have a substantial role in eczema management. Available in various presentations, there is a range of steroid potencies from mild, moderate, potent, to very potent. Long term use is discouraged due to risk of local adverse effects such as atrophy (degeneration of cells), striae (stretch marks) and telangiectasia (broken or stretched blood vessels). Steroids are primarily anti-inflammatory agents. Any antipruritic effect is secondary to the anti-inflammatory action<sup>16</sup> and tends to lag behind other parameters<sup>17</sup>.</p>	<p>Itch reduction qualities of topical steroids are secondary to their anti-inflammatory properties, so response is slow</p>
<p><b>Oral H<sub>1</sub> antihistamines</b>, both sedating and non-sedating, have been used to treat pruritus associated with eczema<sup>10, 16, 17</sup>. Although effective to some degree, use may be limited by drowsiness and efficacy may be largely attributed to their central sedating effect. Non-sedating antihistamines appear to be less efficacious at relieving itch than sedating ones, which may support this concept<sup>18, 19</sup>.</p>	<p>Oral antihistamines are effective to some degree but this may be attributed to their central sedating effect</p>
<p><b>Many Topical antihistamines</b> have been largely disappointing in terms of efficacy and have the tendency to produce contact sensitisation<sup>7, 8</sup>. They have only limited, short-term use in dermatology, as do topical <b>anaesthetics</b>, for similar reasons. Phototoxic and photoallergic reactions may also occur.</p>	<p>Efficacy of many topical antihistamines and anaesthetics are largely disappointing, and have a tendency to produce contact sensitisation</p>

**Doxepin hydrochloride**, although commonly used in oral forms to treat depression and anxiety, has also been used systemically for its antipruritic properties in a variety of itching conditions, notably chronic urticaria<sup>20</sup>.

The exact pharmacological action responsible for this effect is unknown but may be related to its potent antagonism of histamine receptor sites. Laboratory studies reveal that doxepin for example has great affinity for H<sub>1</sub> and H<sub>2</sub> receptors<sup>21</sup>. In fact within this class, doxepin is the most potent H<sub>1</sub> and H<sub>2</sub> antagonist identified<sup>22</sup> and exceeds other histamine antagonists such as hydroxyzine, diphenhydramine and even the H<sub>2</sub> antagonist, cimetidine<sup>8, 23</sup>. Doxepin also acts on muscarinic and other receptors<sup>24</sup>. Topical solutions of doxepin and amitryptiline have been shown to be effective antipruritic agents<sup>25</sup>.

Application of topical doxepin produced a significant elevation of itch threshold in volunteers<sup>25</sup>. Extensive patch testing in over 500 subjects showed a low risk of irritation and sensitisation<sup>26</sup>.

The combination of clear efficacy and a low potential for adverse effects lead to the pharmaceutical and clinical development of doxepin cream 5% (**Xepin**), a specific treatment for the management of pruritus associated with eczema.

**Xepin 5% w/w Cream** antagonises known mediators of itch at the H<sub>1</sub> and H<sub>2</sub> receptors, and potentially the muscarinic receptors.

Efficacy and product safety proven in clinical trials studying in excess of 1200 patients

## Pivotal Efficacy Studies – Doxepin Cream (Xepin)

The major pivotal studies<sup>27, 28</sup> performed for regulatory approval employed the same study protocol, enrolling patients with at least moderately severe pruritus, into a double blind comparison study with vehicle. The active or placebo cream was applied four times daily for eight days, with patients evaluated at baseline (day 1), days 2, 4 and 8. Patients recorded responses to treatment on visual analogue scales, for pruritus relief (VAS-PR, vertical) and for pruritus severity (VAS-PS, horizontal) (fig.1).

The investigator recorded pruritus severity on a four point scale and physician's global evaluation (PGE) for pruritus relief on a five point scale. The investigator also recorded eczema severity and eczema relief plus other parameters including adverse events (table 1).

**Table 1 – Study evaluation**

Patient	Investigator
VAS Pruritus Relief	Pruritus Severity Rating
VAS Pruritus Severity	PGE for Pruritus Relief
	Eczema Severity
	Eczema Relief
	Quality of Life
	Concomitant medications
	Adverse Events

**Fig. 1 - VAS for pruritus relief and severity**



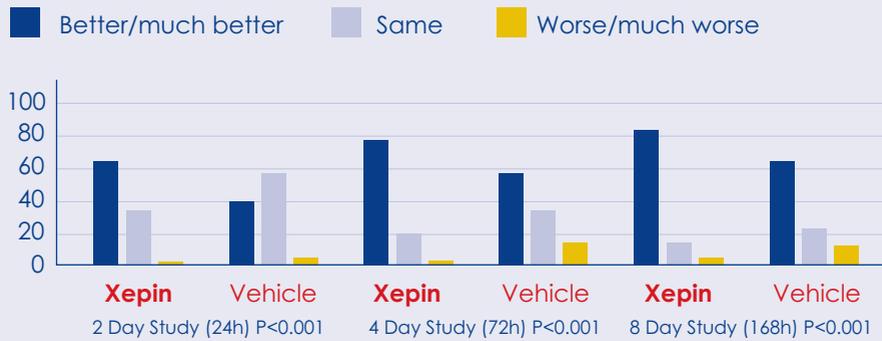
The two largest studies contained 352<sup>27</sup> and 232<sup>28</sup> patients respectively, and both delivered fundamentally similar results. The evaluable patient populations in these studies were grouped by diagnosis: atopic dermatitis, 167 and 88 patients; lichen simplex chronicus, 74 and 59 patients; other eczemas, 101 and 70 patients respectively.

In atopic eczema patients at 24hrs; PGE for pruritus relief was 63% (fig.2<sup>27</sup>) and 60% (fig.3<sup>28</sup>) 'better or much better' for doxepin (listed as **Xepin** in the graphs) and reached 85% and 80% respectively at eight days.

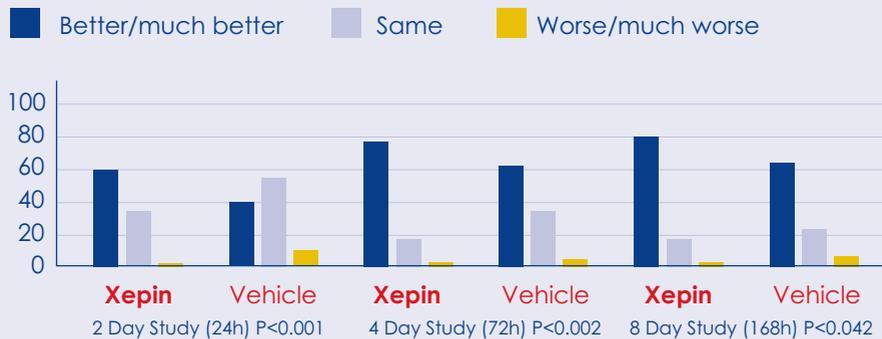
Compared with vehicle, these results were significantly in favour of **Xepin** throughout the study. Results for lichen simplex chronicus (LSC) were similar to those of atopic eczema (AE), demonstrating early indications of the rapid onset of relief, provided by the active ingredient in **Xepin Cream**.

Clear benefit in favour of **Xepin Cream** was also reported by patients for pruritus relief in both studies for both AE<sup>27</sup> and LSC<sup>28</sup> with reductions of 54 % and 55% respectively. These results are presented graphically in Fig.4 and Fig.5.

**Fig. 2 – Percent of patient response: 352 patient trial – Atopic Eczema<sup>27</sup>**



**Fig. 3 – Percent of patient response: 232 patient trial – Atopic Eczema<sup>28</sup>**

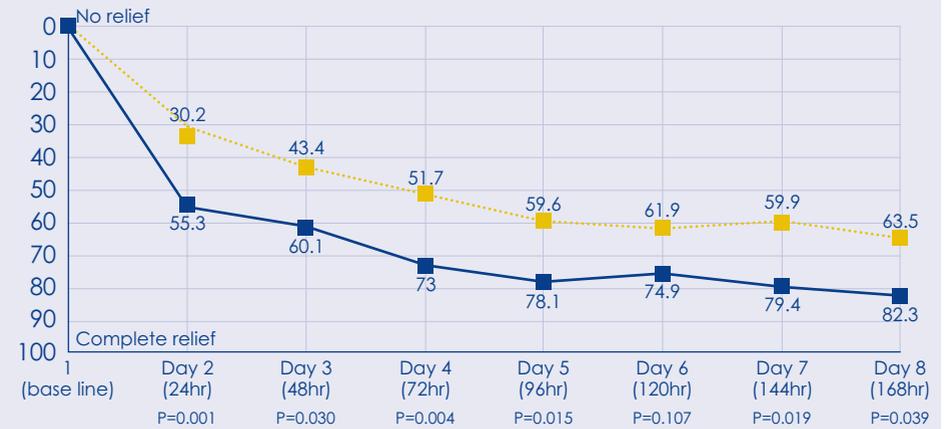


The commonest adverse events reported were application site reactions e.g. stinging/burning, drowsiness and dry mouth which are discussed later under 'side effects'.

**Fig. 4 – Mean percent reduction in pruritus intensity: 352 patient trial – Atopic Dermatitis<sup>27</sup>**



**Fig. 5 – Mean percent reduction in pruritus intensity: 232 patient trial – Lichen Simplex Chronicus<sup>28</sup>**



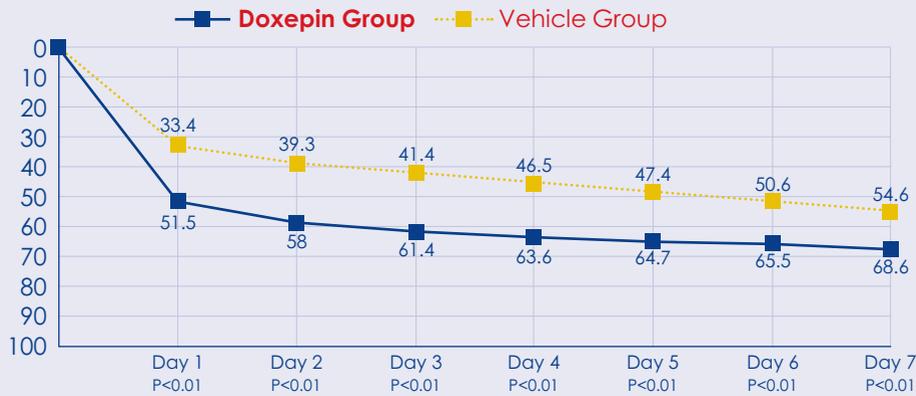
### Further Efficacy Studies – improvement in eczema

Such was the interest in topical doxepin cream that a group of US dermatologists formed the Doxepin Study Group. Two publications from this group<sup>29, 30</sup>, using protocols similar to the double blind vehicle controlled protocol of the pivotal studies, involved 270<sup>29</sup> and 309<sup>30</sup> patients respectively, with mixed eczemas, associated with moderate to severe pruritus.

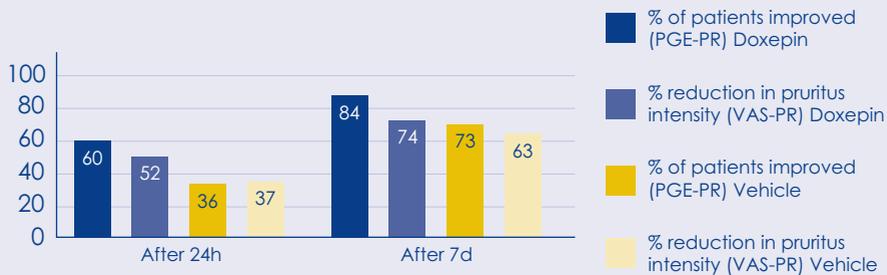
In both studies the PGE for pruritus relief showed significant advantage for doxepin cream at 24 hours (60%<sup>29</sup> and 60%<sup>30</sup> of patients respectively) and this advantage was maintained to day seven, the final day (84%<sup>29</sup> and 84%<sup>30</sup> of patients).

The visual analogue scales for pruritus relief (VAS-PR) rated by patients, showed significant advantage after 24hrs for doxepin cream with 52% reduction in severity in both studies progressing to 68%<sup>29</sup> and 75%<sup>30</sup> reduction at day seven. Adverse reactions followed the previously observed profile consisting of site reactions, drowsiness and dry mouth. These two studies showed remarkably similar data profiles, and examples of the results are shown in Fig.6 and Fig.7.

**Fig. 6 – VAS-PR in atopic dermatitis patients. Significant improvement in favour of Doxepin observed at each day<sup>29</sup>**



**Fig. 7 – % improved patients on PGE for pruritus relief and corresponding reduction in VAS-PR for Doxepin and vehicle after 24h and 7 days<sup>30</sup>**



Both these studies also monitored eczema severity, primarily to examine whether doxepin cream caused worsening of the eczema, rather than as a sophisticated measure of clinical improvement.

In one study<sup>30</sup>, there was a strong trend in favour of doxepin over vehicle; in the other<sup>29</sup>, there was a clear statistical improvement in favour of doxepin cream at day seven.

**It is thus thought that doxepin cream may have a salutary action on eczema. As doxepin cream provides rapid symptomatic relief of itch there may also be benefit from concomitant use with steroids, allowing the use of lower potency steroids and/or shorter treatment periods, since the control of pruritus is not solely dependent on the corticosteroid<sup>30</sup>.**

### Early onset of relief and lack of rebound on cessation

The early onset of pruritus relief observed in the first 24hrs of treatment, stimulated another group to investigate the onset of action of doxepin and also to ascertain whether there was a pruritus 'rebound' on cessation of treatment<sup>31</sup>.

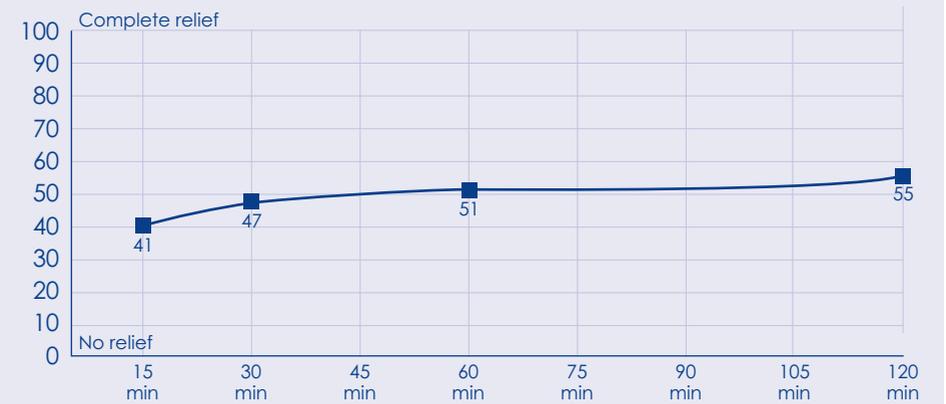
120 patients with atopic eczema or lichen simplex chronicus affecting less than 25% of body surface area (BSA), with moderate to severe pruritus, were treated with doxepin cream 5% *qds* for seven days in a single-blind phase. Following randomisation, patients then entered a further seven day double-blind phase, receiving either active or vehicle.

In the first phase, patients assessed pruritus severity and pruritus relief, as in other studies, using visual analogue scales, after 15, 30, 60 and 120 minutes on day one and nightly thereafter to day seven.

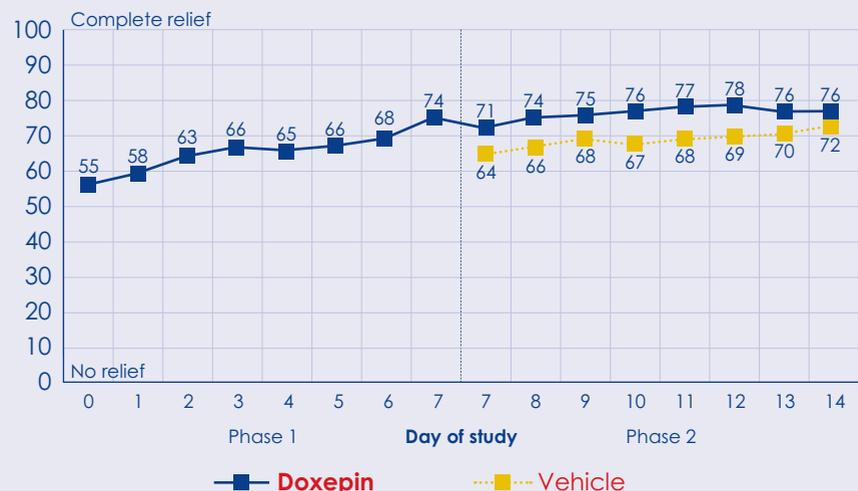
It was observed that just 15 minutes after application of doxepin, 75% of subjects reported significant reduction compared with baseline, for VAS-PS. This increased to 84% at 120 minutes. Similarly, VAS-PR reduction was significant after 15 minutes, which again continued through 120 minutes (fig.8). These results were maintained for the seven day duration of the second phase of the study.

Investigators recorded significant improvement in both pruritus severity and PGE-PR at day seven.

**Fig. 8 – Onset of action shown by effect on mean % VAS-PR compared with baseline (P,0.001) from 15 mins onwards<sup>31</sup>**



**Fig. 9 – Effect of topical Doxepin on mean % change from baseline in VAS-PR. No rebound on cessation (vehicle group) at day 7<sup>31</sup>**



A sleep assessment was included on days 0, 7 and 14 to examine the amount of sleep interference caused by pruritus during the preceding week. This showed a significant improvement at day seven, which was maintained at day 14.

Eczema severity was assessed by the investigators on day 7 and on day 14 on a range of signs and symptoms. There were significant improvements in all parameters except oozing on day 7. Excoriations improved particularly, which might be expected due to reduced scratching as itch subsided.

No rebound effect was noted in the double-blind phase when those discontinuing doxepin treatment were allocated to vehicle (fig.9). Patients switched to vehicle continued to enjoy pruritus relief to day 14, the end of the study. However, VAS-PR and VAS-PS showed greater improvement for those continuing on topical doxepin. PGE-PR continued to improve during the second phase in both treatment groups but was significantly improved from day 7 to day 14 only in the doxepin group. Adverse reactions were mild to moderate. The site reactions and somnolence adverse events decreased throughout the study. This important study demonstrates that onset of action of topical doxepin cream is extremely rapid, producing significant reduction in pruritus within 15 minutes.

Efficacy builds and continues over the first seven days and up to the fourteenth day of treatment. The authors suggested that these results support the concept previously advanced<sup>31</sup>, that concomitant use of topical doxepin may through its own rapid effect on itch help reduce the need for high potency topical steroids and avoid their over-use.

There is no rebound on cessation unlike that observed sometimes with topical steroids. Further, eczema severity is reduced by topical doxepin cream and that it is safe to use for 14 days continuously.

## Doxepin and topical steroids

A small double-blind study comparing the efficacy of topical doxepin cream with 1% hydrocortisone *qds*, in atopic and contact eczema, was carried out in the UK<sup>32</sup>. 49 evaluable patients completed the eight day study.

Patients completed VAS-PR and VAS-PS assessments and the investigators recorded pruritus severity and PGE for pruritus relief. Both treatments were equally effective at the end of the eight day course but doxepin was almost twice as effective as hydrocortisone in reducing pruritus during the first few days of treatment. VAS-PS fell just short of significance on day eight.

This study may have lacked statistical power but showed a striking difference in the first four days, for doxepin. Adverse reactions were principally somnolence and site reactions.

A large study (349 patients)<sup>33</sup> examined the effect of adding topical doxepin to topical steroid therapy in atopic dermatitis. This eight day multi-centre double-blind parallel design study randomised patients to four groups receiving identical vehicle based creams containing triamcinolone 0.1%; triamcinolone 0.1% plus doxepin 5%; hydrocortisone 2.5% and hydrocortisone 2.5% plus doxepin 5%.

The creams were applied four times daily. Patients completed VAS-PS and VAS-PR assessments one week before entry and during the study on days 2, 3, 4 and 8. At each visit the investigator made a global evaluation of pruritus relief (PGE-PR) and rated the overall change in dermatitis.

Both VAS-PS (Table 2) and VAS-PR showed significant improvement throughout the study when doxepin was added to either steroid. The PGE-PR showed that addition of doxepin to either steroid significantly improved itch relief over that of the topical steroid alone. The physicians evaluation of dermatitis relief showed that addition of doxepin to the steroid brought more rapid improvement in the eczematous condition over the first few days. The most common adverse effect was stinging or burning, which generally subsided during the study. The addition of doxepin to the steroid had little effect on this. Drowsiness was more common in the steroid plus doxepin groups.

The authors noted that topical steroids are generally effective over days or weeks in ameliorating the condition but their effect on itch is secondary to their anti-inflammatory action. The addition of topical doxepin to topical steroid therapy provided faster and more substantial reduction in itch. This should permit shorter courses of topical steroids than when they are used alone.

**Table 2 – Mean % reduction in VAS-PS compared with baseline<sup>33</sup>**

Treatment	Day 1 (12h)	Day 2 (24h)	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Doxepin/hydrocortisone	31.6*	43.8*	57.7*	61.9*	66.3*	68.3*	65.4*	68.2
Hydrocortisone	8.0	27.3	42.3	42.5	46.1	47.2	51.4	61.4
Doxepin/triamcinolone	22.4	45.9*	62.6	70.4	78.1	82.5*	86.5*	91.3*
Triaconolone	10.7	29.5	53.1	61.0	67.5	70.6	73.9	79.1

\*combination significantly better than steroid alone at these time points (p from 0.05 to <0.001)

## Side effects

Doxepin Cream has been closely studied during its clinical development. As is common with all medications, a long list of adverse reactions has been noted as data has been accumulated. Many of these are of very low incidence and differ little between doxepin and vehicle groups.

Table 3 summarises the most common adverse experiences reported in the two large pivotal studies reviewed earlier<sup>27, 28</sup>. These incidences are broadly in line with the findings of subsequently published studies.

Overall, **Xepin Cream** (doxepin cream 5%) has been shown to be well tolerated and adverse effects mild and transient. Extensive clinical usage in the United States (as Zonalon cream) where hundreds of thousands of prescriptions have been filled and on a smaller scale here in the UK, where **Xepin** first became available in 1999, have shown doxepin cream to have a favourable risk benefit profile, by-passing the well-known side effects of topical steroids, which remain the most widely used treatment for eczema and pruritus currently.

Of the adverse experiences observed, application site reactions (stinging and burning), and drowsiness warrant particular comment.

**Table 3 — Adverse experience<sup>27,28</sup>**

Adverse Experience	% of patients	
	Xepin Cream (n=330)	Vehicle (n=334)
Burning/stinging at application site	21.0%	16.0%
Drowsiness	22.0%	2.0%
Dry mouth/dry lips/thirst	9.7%	1.2%
Pruritus exacerbation	4.0%	6.0%
Eczema exacerbation	3.0%	2.4%
Fatigue/tiredness	3.0%	1.6%
Dizziness/vertigo	2.1%	0.9%
Mental/emotional changes	1.8%	0.3%
Oedema	1.5%	0.0%
Taste changes	1.5%	0.3%
Headache	1.0%	4.2%
Numbness	1.0%	0.0%

## Burning and stinging

Application site reactions were the commonest reported adverse experience in the pivotal studies<sup>27, 28</sup> and have remained so in subsequent investigations<sup>29-32</sup>. In the study of topical doxepin with topical steroids<sup>31</sup>, drowsiness overtook site reactions.

As shown in Table 3, topical doxepin had broadly similar incidences of site reaction as the vehicle. Given that the studies were on patients with moderate to severe eczemas, whose skin may tend to be broken, these results are perhaps not surprising.

The stinging and burning was generally of mild intensity. In the pivotal studies, the intensity was greatest on day one and abated after a mean of 2.1 days. Few patients (1.2%) withdrew from these studies due to this effect.

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(doxepin hydrochloride)

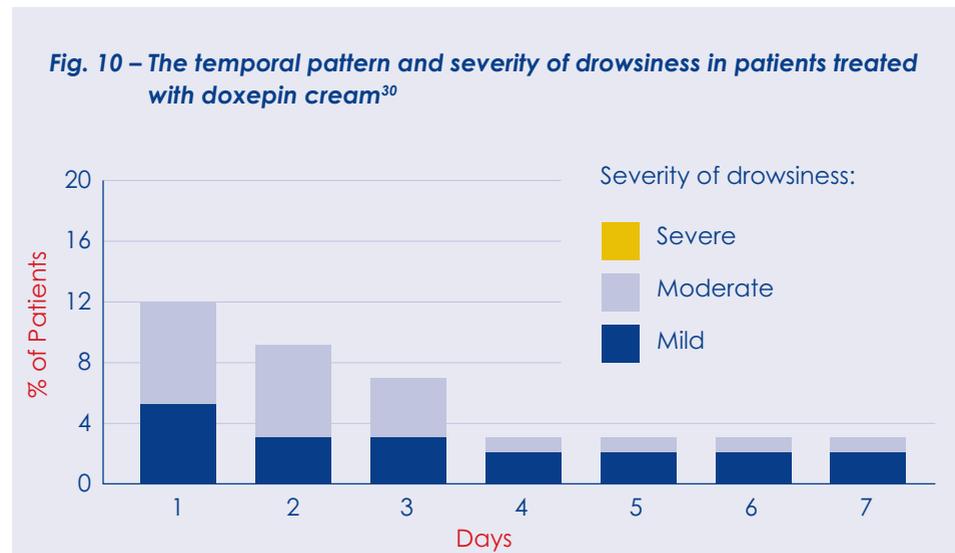


Stop the itch-scratch cycle  
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## Drowsiness

Drowsiness has been consistently reported in studies with topical doxepin. In Table 3, 22% of subjects reported drowsiness at some stage during the eight day pivotal studies. This tended to be mild and lasted for a short time. A meta-analysis of the studies<sup>34</sup> showed the mean duration of drowsiness was 3.6 days, evidencing itself at the start of the study, declining over the course of treatment and being uncommon by the end of the study. Drowsiness resulted in 15 withdrawals in the pivotal studies. The temporal nature of drowsiness is well illustrated by the large patient series of Drake and Millikan<sup>30</sup> which is represented here in Fig.10.



Drowsiness seems to be more common with increasing body surface area (BSA) treated. Drowsiness is a difficult parameter to follow in clinical studies, particularly with patients who may be suffering sleep disturbance as itching is often worse in bed, at night. It has already been noted that the older sedating oral antihistamines may be more effective than the newer non-sedating preparations<sup>18, 19</sup>. Drowsiness, or sleep promotion is not entirely undesirable if itching has interfered with sleeping. Patients who drive or operate machinery should of course be made fully aware of any such potential.

What has also been resolved in data analysis<sup>34</sup>, is that drowsiness and efficacy are not related and that the antipruritic effect is a peripheral action rather than central. In fact, patients who had no drowsiness had if anything greater improvement of their itching compared with those who were drowsy. As already noted, the effect is generally mild and transient, resolving rapidly during treatment.

## Irritation and sensitisation

Patch testing and photosensitivity studies were performed during the clinical development programme of doxepin cream, with over 500 subjects with normal skin being subject to testing. The key findings of those studies<sup>35</sup> being presented here in table 4, and which indicate a low potential for irritation and sensitisation.

**Table 4 – Irritation and sensitisation<sup>35</sup>**

Study	No. patients	Application schedule and method	Result
Modified Draize-Shelanski-Jordan patch test	494	3 tests of topical 2% and 5% doxepin creams; one every 48 hrs. Re-challenge patching after rest period	No evidence of irritant or allergic response. One subject with mild reaction (0.2% sensitisation)
Phototoxicity	10	24hr monitoring period	No adverse events
Photocontact	26	48hr monitoring period	No adverse events
Photocontact	29	Tested then re-challenged on day 29 and re-evaluated at days 31-33	Six minor adverse reactions but none light induced. No evidence of phototoxic or photoallergic responses
Phototoxicity	11		

Following the commercial introduction of doxepin cream (as Zonalon) in the USA, Shelanski et al<sup>36</sup> undertook a study to review cutaneous reactivity to a group of recently marketed dermatological products including doxepin cream, calcipotriene, metronidazole, ketoconazole, clobetasol, mupirocin, oxiconazole, terbinafine and doxepin vehicle cream. 108 healthy adult volunteers took part in double-blind repeated insult patch test procedure.

The results suggested that all the preparations were safe and had low risks of clinically significant irritation or sensitisation. The authors noted however that; "Virtually every topically applied product or chemical ingredient has some potential to produce irritant or sensitization reactions. When there is exposure of a sufficiently large patient population, even products with a low irritant or sensitization potential will be associated with a number of adverse cutaneous reactions."

This common sense view has proven to be the case with doxepin cream which with many hundreds of thousands of prescriptions written in the USA and many tens of thousands in the UK since its introduction, has resulted in some reports of contact irritation and sensitisation. These have been infrequent.

Patch testing on a series of 97 patients with various pruritic dermatoses<sup>37</sup> showed that doxepin was a sensitiser in 13 out of 17 reactors. However, the authors noted that use of the product had ranged from a few days up to a year, with reference to weeks and months use in others.

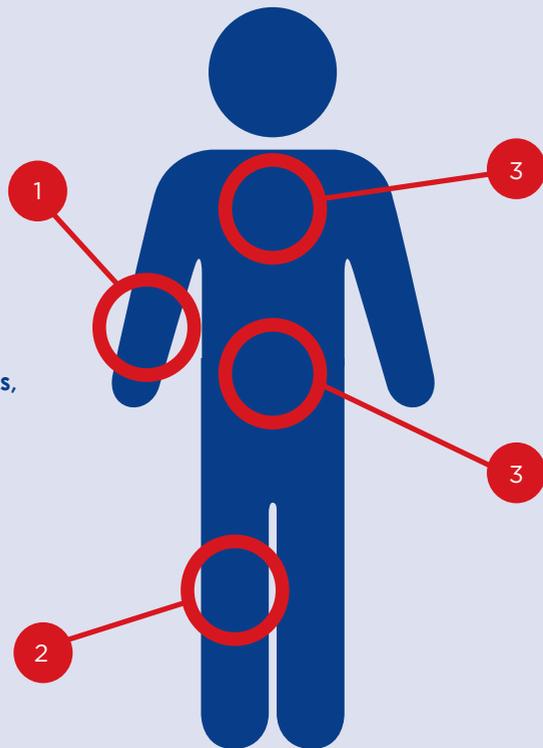
It should be emphasised that the recommended treatment for **Xepin Cream** is 3/4 times daily to not more than 10% BSA (fig. 11). Study data only exists for use in up to 14 days and it has been noted that more or less maximum response is achieved in the first seven days of treatment.

**Fig. 11 – Body surface area (BSA) guide**

10% of the body area is roughly equal to:

- 1 - one whole arm
- 2 - the front or back of a leg
- 3 - half of the torso

This 10% can be made up by several smaller hot spots (e.g. your knees, face or hands)



## Practical Considerations

Experience from the extensive clinical studies and post-marketing monitoring shows that **Xepin Cream** is an effective and largely trouble-free medication. Patients find the preparation cosmetically acceptable and appreciate the rapid onset of pruritus relief.

It is important that the medicine is used appropriately. Stinging and burning at the application site, drowsiness and dry mouth have been shown to occur in the first few days of treatment and are transient, abating over a few days. Drowsiness is generally linked to excessive use of **Xepin Cream** in terms of quantity applied, BSA covered and extended treatment periods.

Whilst the SmPC does not impose a treatment limitation, it should be remembered that studies have covered continuous treatment periods only up to 14 days at a *qds* dosage. The clinical data shows that pruritus relief occurs rapidly from day one and approaches its maximum after four to five days, being maintained throughout the treatment period. **Xepin Cream** is generally used for relatively short treatment periods at the start of therapy or in acute flare-ups.

**Xepin Cream** is approved for adults and children over 12 years old. Prescribers should be aware of the anticholinergic activity of the preparation and the potential drug interactions which have been well described in relation to oral doxepin therapy.

### Effective<sup>31</sup>

75% of patients have a significant reduction in itch after 15 minutes

### Tolerable

Does not contain steroids, parabens or perfume

## Place In Eczema Therapy And Management

Given Xepin Cream's rapid effect, it has a particular place in the management of eczema. It may be used alone to bring intense itch under control, being superseded by a less potent topical steroid to manage residual inflammation or even an emollient for longer term management, if appropriate. There is also a sound rationale for concomitant use with a topical steroid, again of lower potency or for a shorter period before transition to an emollient alone.

Eczema flare-ups may also provide an appropriate opportunity for use of Xepin Cream, with a view to early return to emollients for maintenance, if needed.

**Cessation of Xepin treatment does not result in rebound itching.**

## Medicines Management – An Effective Use of NHS Resource

Research carried out in 2009 indicated that 80% of adult eczema patients have difficulty falling asleep because of the itch associated with their eczema<sup>38</sup>. This suggests that despite the use of emollients and steroids there are still significant itch related problems in the vast majority of patients – indicating an unmet need.

Current treatment regimens are failing to control this condition so it is worth looking into alternative medications.

A review of the global literature investigating the use of all topical antihistaminic agents by Cocks-Eschler & Klein<sup>1</sup> in 2010 found that of the 19 trials published between January 1950 and September 2009 only 4 trials were of a size and suitable design to confirm the efficacy of the product studied in the relief of pruritus. All 4 trials studied topical doxepin.

The authors concluded that “Based on the literature, topical doxepin is the only topical antihistaminic agent supported by large, randomised controlled clinical trials in pruritus relief”<sup>1</sup>.

Eczema causes considerable disruption to the lives of adult sufferers and is cited as the cause of loss of concentration and absenteeism from work plus straining of family relations. Many of these have direct effects on the social care and employment prospects for the patient with knock-on effects on the economy.

The addition of **Xepin Cream** into the treatment regime at an outbreak of an eczema flare would have the following consequences based on the literature:

- **Rapid Control of itch leading to better sleep.**
- **Reduction in scratching, leading to less severe excoriations and faster healing of lesions.**
- **Reduction in either the use or potency of topical steroids.**
- **Faster control of symptoms leading to reduced disruption to working life.**

### Lifestyle



Controlling flare-ups.

Start with identifying and avoiding eczema triggers and irritants to the skin

### Emollients



These help to rehydrate the skin and should be used regularly



A 30g tube of **Xepin Cream** costs the NHS £11.70. If it is applied to a maximum of 10% of the body surface area (for example the flexures of the arms and legs) per application then this tube would last 20 applications – probably more than would be needed to cover the average eczema flare. At a cost of 39p per gram, **Xepin** is more expensive than an equivalent tube of steroid cream or emollient but as a rapid resolver of itch in adult eczema there is no other topical medication that can clinically demonstrate equal or better performance<sup>1</sup>.

**Xepin is therefore unique in its class and, as such, represents an effective use of NHS resource.**

## Summary

Pruritus is the principal symptom of eczema and a cause of enormous discomfort to patients. The itching can be intolerable and has a profound effect on quality of life. The establishment of the itch-scratch cycle worsens matters making the condition chronic, causing lichenification, excoriations and possible infection.

Traditional antipruritic therapies have been sub-optimal both in terms of efficacy and side-effects.

**Xepin Cream (doxepin 5% w/w)** has been shown to provide effective, rapid relief of itch associated with eczema. It has also been shown to add benefit when used with topical steroids. Steroid sparing may thus be achieved through shorter courses of treatment perhaps with lower potency steroids, reducing the well-known potential risks of prolonged topical steroid therapy. Side effects, principally drowsiness, are mild and transient. Allergic sensitisation is uncommon and usually associated with excess use.

**Xepin cream offers the possibility of improved management of eczema through a direct effect on its most troublesome symptom, itch.**

Can be used simultaneously<sup>1</sup>

### Xepin 5% w/w cream



Apply specially formulated doxepin cream to stop the itch-scratch cycle



### Steroid Creams



Different strengths available to tackle the inflammation



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## Summary of Product Characteristics

1. **NAME OF THE MEDICINAL PRODUCT** Xepin 5% w/w Cream
2. **QUALITATIVE AND QUANTITATIVE COMPOSITION** Doxepin hydrochloride 5% w/w
3. **PHARMACEUTICAL FORM** Cream for topical application to the skin.
4. **CLINICAL PARTICULARS**
  - 4.1. **Therapeutic indications** For the relief of pruritus associated with eczema.
  - 4.2. **Posology and method of administration: Adults and children over 12 years.** A thin film of Xepin should be applied three to four times daily, to the affected area only. Clinical experience has shown that drowsiness is significantly more common in patients applying cream to more than 10% of the body surface area, therefore, the maximum coverage should be less than 10% of body surface area. For an average sized patient, this would equate to 3g of Xepin per application and not more than 12g of Xepin per day. If excessive drowsiness does occur, it may be necessary to reduce the number of applications, the amount of cream applied and/or the percentage of body surface area treated. Occlusive dressings or clothing may increase the absorption of any topically applied drug, including Xepin; therefore, caution must be exercised when utilising occlusive dressings.  
**Children under 12 years** There are insufficient data to enable dosage recommendations to be made for children.  
**Elderly** There are no specific dosage recommendations for elderly patients.
  - 4.3. **Contraindications** Xepin is contra-indicated in individuals who have shown previous hypersensitivity to any of its components.
  - 4.4. **Special warnings and precautions for use** Drowsiness may occur with the use of Xepin. Clinical trial data demonstrate that drowsiness is observed principally in patients receiving treatment to greater than 10% of body surface area and that drowsiness is transient, usually remitting after the first few days of treatment. Patients should, therefore be warned of this possibility and cautioned against driving or operating machinery if they become drowsy while being treated with Xepin. Patients should also be warned that the effects of alcohol could be potentiated. In view of the known adverse effects of orally administered doxepin hydrochloride, Xepin should be used with caution in patients with the following conditions: glaucoma, a tendency to urinary retention, severe liver disease, mania, or severe heart disease including those prone to cardiac arrhythmias. Cetyl alcohol may cause local skin reactions (e.g. contact dermatitis).
  - 4.5. **Interactions with other medicinal products and other forms of interaction** Alcohol ingestion may exacerbate the potential sedative effects of Xepin particularly in those individuals who use alcohol excessively. MAO inhibitors should be discontinued at least two weeks prior to the initiation of treatment with Xepin since serious interactions have been reported between orally administered doxepin hydrochloride and MAO inhibitors. As doxepin is metabolised via hepatic microsomal enzymes, care should be taken when co-prescribing any other medicines which are also metabolised by this route. Caution should also be exercised in patients being treated with cimetidine since it has been found to affect serum concentrations of orally administered tricyclic antidepressants, such as doxepin hydrochloride. Oral doxepin hydrochloride is known to interact with sympathomimetic agents and may increase the risk of arrhythmias and hypotension or hypertension with general and local anaesthetics. In view of the small but noteworthy amount of systemic absorption following topical administration of Xepin (see 5.2) caution should be exercised with these agents.
  - 4.6. **Fertility, pregnancy and lactation** There is inadequate evidence of safety in human pregnancy and lactation. Reproductive studies performed in rats, rabbits, monkeys and dogs with oral doxepin showed no evidence of harm to the animal foetus. As with all drugs, Xepin should only be used in pregnancy and lactation if, in the clinician's judgement, the benefits outweigh the risks.
  - 4.7. **Effects on ability to drive and use machines** Patients should be advised not to drive a motor vehicle or operate machinery whilst using Xepin. Particular caution should be exercised during the first few days of treatment.
  - 4.8. **Undesirable effects** Drowsiness has been reported in clinical trials, with an incidence of 12-19%. However, it is generally of mild to moderate severity and of short duration. Limiting the body surface treated to less than 10% is important in minimising the risk of drowsiness.

Local adverse reactions have been reported with the use of Xepin and may occur more frequently with the use of occlusive dressings. Local reactions, in decreasing order of frequency, include burning, stinging, irritation, and tingling and local rash.

Systemic effects which have been observed with orally administered doxepin hydrochloride are rarely observed with topical Xepin. These may include anticholinergic effects (dry mouth, changes in taste, dry eyes, blurred vision, urinary retention); central nervous system effects other than drowsiness (headaches, fever, dizziness); and gastrointestinal effects (nausea, indigestion, vomiting and diarrhoea or constipation). Cases of suicidal ideation and suicidal behaviours have been reported during oral doxepin hydrochloride therapy or early after treatment discontinuation.

**Reporting of suspected adverse reactions** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme ([www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard)).

- 4.9. **Overdose Symptoms** Symptoms of overdosage of orally administered doxepin hydrochloride include an increase of any of the reported reactions, primarily excessive sedation and anticholinergic effects such as blurred vision and dry mouth. Other effects may be pronounced tachycardia, hypotension and extrapyramidal symptoms, but these are unlikely to be seen following topical use.

**Treatment** Excess cream should be washed off immediately. Treatment of overdosage is essentially symptomatic. Supportive therapy may be necessary if hypotension and/or excessive sedation occur.

### 5. PHARMACOLOGICAL PROPERTIES

**5.1. Pharmacodynamic properties** Doxepin hydrochloride is a dibenzoxepin tricyclic compound structurally related to tricyclic antidepressant drugs such as amitriptyline. Doxepin hydrochloride has potent H<sub>1</sub> and H<sub>2</sub> receptor blocking actions. Histamine is considered to be an important chemical mediator in the pathogenesis of pruritus. Histamine blocking drugs appear to compete at histamine receptor sites and inhibit the biological activation of histamine receptors.

**5.2. Pharmacokinetic properties** There is a small but noteworthy amount of systemic absorption following topical administration, with wide inter-individual variations in plasma levels and in the handling of doxepin. Orally administered doxepin undergoes extensive first-pass metabolism but topical administration avoids this initial clearance. Plasma doxepin levels following topical administration are generally low, although in a few subjects they may approach the lower limit of the therapeutic range (for depression) of orally administered doxepin.

**5.3. Preclinical safety data** Doxepin, which is given orally as a tricyclic antidepressant, has been shown to have potent antihistamine activity in animal models. Acute and chronic toxicity of doxepin has been fully evaluated following oral administration to rats and dogs, and these studies revealed the expected effects for this class of drug.

The local toxicity of Xepin has been studied in healthy volunteers. It has been shown to be neither irritant nor allergenic, although it caused local irritation in a small number of cases.

### 6. PHARMACEUTICAL PARTICULARS

**6.1. List of excipients** Inactive ingredients in the cream are; sorbitol solution 70% (crystallising), cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG 100 stearate, white soft paraffin, benzyl alcohol, titanium dioxide E171 and purified water.

**6.2. Incompatibilities** None known

**6.3. Shelf life** 3 years

**6.4. Special precautions for storage** Do not store above 25°C

**6.5. Nature and contents of container** Aluminium tubes with S-22 epoxyphenolic lining and a high density polyethylene spiked screw cap containing 30g, 60g or 120g Xepin A 6.0g pack is available as a professional sample.

**6.6. Special precautions for disposal** Not applicable.

**7. MARKETING AUTHORISATION HOLDER** Cambridge Healthcare Supplies Ltd, Unit 1 Chestnut Drive Wymondham, Norfolk, NR18 9SB

**8. MARKETING AUTHORISATION NUMBER** PL 16794/0008

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** 15th October 2002

**10. DATE OF REVISION OF THE TEXT** March 2015

# Xepin

5% w/w Cream (doxepin hydrochloride)



As recommended by

**BAD**

(British Association  
of Dermatologists)

**Guidelines for  
generalised pruritus,  
2018<sup>1</sup>**

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