

## Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group

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### Summary

Psoralen photochemotherapy [psoralen ultraviolet A (PUVA)] plays an important part in dermatological therapeutics, being an effective and generally safe treatment for psoriasis and other dermatoses. In order to maintain optimal efficacy and safety, guidelines concerning best practice should be available to operators and supervisors. The British Photodermatology Group (BPG) have previously published recommendations on PUVA, including UVA dosimetry and calibration, patient pretreatment assessment, indications and contraindications, and the management of adverse reactions.<sup>1</sup> While most current knowledge relates to oral PUVA, the use of topical PUVA regimens is also popular and presents a number of questions peculiar to this modality, including the choice of psoralen, formulation, method of application, optimal timing of treatment, UVA regimens and relative benefits or risks as compared with oral PUVA. Bath PUVA, i.e. generalized immersion, is the most frequently used modality of topical treatment, practised by about 100 centres in the U.K., while other topical preparations tend to be used for localized diseases such as those affecting the hands and feet. This paper is the product of a recent workshop of the BPG and includes guidelines for bath, local immersion and other topical PUVA. These recommendations are based, where possible, on the results of controlled studies, or otherwise on the consensus view on current practice.

*Key words:* photochemotherapy, psoralens, PUVA, therapy

### Pretreatment assessment

Recommendations concerning pretreatment assessment and contraindications for topical psoralen photochemotherapy [psoralen ultraviolet A (PUVA)] are largely the same as those published for oral PUVA.<sup>1</sup> However, topical PUVA is preferable to oral PUVA in the following circumstances.

- 1 In patients with hepatic dysfunction.
- 2 In patients with gastrointestinal disturbance

and where absorption is uncertain, e.g. after ileostomy.

- 3 In patients with cataracts.

- 4 Where compliance with eye protection may be poor.

- 5 To permit shorter irradiation times (particularly in black patients, where very high UVA doses are otherwise needed, and in claustrophobic individuals and children).

- 6 Where psoralen–drug interactions are anticipated, e.g. with warfarin.

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**Table 1.** (a) Generalized conditions treated with topical psoralen ultraviolet A (PUVA)<sup>a</sup>

Generalized dermatoses	Topical PUVA	Study methodology	No. of patients
Atopic dermatitis	8-MOP ointment	Case series <sup>41</sup>	114
Lichen planus	TMP bath/ointment	Case series <sup>12</sup>	75
	TMP bath	Case series <sup>13</sup>	19
	8-MOP bath	Case series <sup>14</sup>	4
	8-MOP bath	Retrospective case comparison <sup>15</sup>	13
	8-MOP bath	Case series <sup>16</sup>	17
Systemic sclerosis and generalized morphea	8-MOP topical lotion	Case report <sup>39</sup>	1
	8-MOP bath	Case series <sup>17</sup>	4
	8-MOP bath	Case series <sup>18</sup>	4
Urticaria pigmentosa	TMP bath	Case series <sup>13</sup>	5
	TMP bath	Case series <sup>19</sup>	19
Mycosis fungoides, Sézary syndrome and parapsoriasis	8-MOP topical	Case series, within-subject control <sup>40</sup>	4
	8-MOP paint/cream	Review <sup>38</sup>	(review)
Vitiligo	8-MOP lotion/cream	Randomized comparison <sup>37</sup>	73
	TMP bath	Case series <sup>20</sup>	13
Polymorphic light eruption	TMP bath	Case series <sup>22</sup>	15
Nodular prurigo	TMP bath/ointment	Case series <sup>12</sup>	63
	8-MOP bath	Case series <sup>21</sup>	10
Prurigo simplex subacuta	8-MOP ointment	Case series <sup>42</sup>	13
Uraemic pruritus	8-MOP oral and bath	Case report <sup>24</sup>	1
Aquagenic pruritus	Bath	Case report <sup>23</sup>	1
	Bath	Case report <sup>25</sup>	1

<sup>a</sup> See text for chronic plaque psoriasis.

(b) Hand and foot dermatoses treated with topical PUVA

Hand and foot dermatoses	Topical PUVA	Study methodology	No. of patients
Hyperkeratotic eczema	8-MOP paint	Randomized double-blind comparison <sup>28</sup>	21
	8-MOP paint	Case series <sup>27</sup>	14
	Psoralen aqueous gel	Case series <sup>31</sup>	2
	8-MOP emulsion	Retrospective case comparison <sup>26</sup>	2
	8-MOP cream	Case series <sup>29</sup>	10
Dyshidrotic eczema	8-MOP paint	Case series <sup>27</sup>	14
Hyperkeratotic psoriasis	Psoralen aqueous gel	Case series <sup>31</sup>	7
	8-MOP ointment/lotion	Case series <sup>30</sup>	14
	8-MOP emulsion	Retrospective case comparison <sup>26</sup>	14
Palmoplantar pustulosis	8-MOP emulsion	Prospective uncontrolled (for topical psoralen) <sup>33</sup>	15
	8-MOP emulsion	Randomized double-blind placebo-controlled <sup>34</sup>	27
	8-MOP emulsion	Retrospective case comparison <sup>26</sup>	9
	8-MOP ointment	Case series <sup>32</sup>	5

TMP, trimethylpsoralen; 8-MOP, 8-methoxypsoralen.

## Indications for generalized immersion bath psoralen ultraviolet A

### Psoriasis

A variety of psoralen concentrations and treatment regimens have been used for generalized plaque psoriasis. Studies of 8-methoxypsoralen (8-MOP) bath PUVA with concentrations ranging from 0.5 to 4.6 mg/L and treatments given two to four times weekly, report clearance in 60–90% of patients (mean 16–21 treatments) and total UVA dose of 25–27 J/cm<sup>2</sup>.<sup>2–4</sup> Treatment with 0.33 mg/L trimethylpsoralen

(TMP) bath PUVA, two to seven times weekly, resulted in a good or excellent response in 92% of patients (mean 18 treatments) and total UVA dose of about 20 J/cm<sup>2</sup>,<sup>5</sup> while another study with a similar TMP regimen found good or excellent results in 67% of 51 treatment courses.<sup>6</sup> The use of 5-MOP bath PUVA is little reported; however, a non-randomized study of 8-MOP and 5-MOP bath PUVA in a small number of patients showed that, at the same concentration (0.0003%), there was no significant difference in efficacy, but 5-MOP appeared more phototoxic and pigmentogenic.<sup>7</sup> Of four comparative studies of oral and

bath PUVA (one TMP, three 8-MOP),<sup>8–11</sup> only one is a prospective randomized trial.<sup>10</sup> All suggested a similar response rate, with clearance being achieved with the same number of treatments. The total UVA dose was three to six times lower with bath PUVA, but as discussed later, this does not necessarily imply reduced carcinogenicity.

Hence, bath PUVA is clearly a useful treatment for chronic plaque psoriasis, and appears equally effective to oral PUVA. In keeping with oral PUVA, however, it should be reserved for second-line therapy.<sup>1</sup> As the above studies have not been designed to examine the most effective protocols our recommendations are based on the consensus current practice of British Photodermatology Group (BPG) members (see later section).

#### *Other disorders*

There is a paucity of evidence concerning the efficacy of bath PUVA in other dermatoses, although there are reports (Table 1a) of its value in lichen planus,<sup>12–15</sup> systemic sclerosis and generalized morphea,<sup>16,17</sup> urticaria pigmentosa,<sup>13,18</sup> mycosis fungoides,<sup>19</sup> polymorphic light eruption,<sup>20</sup> prurigo simplex subacuta,<sup>21</sup> nodular prurigo,<sup>12,22</sup> aquagenic pruritus,<sup>23,24</sup> and lymphomatoid papulosis.<sup>25</sup>

In the absence of controlled studies to examine the efficacy of bath PUVA in generalized disorders other than chronic plaque psoriasis, we suggest that a common sense approach is to try a course of bath PUVA in the above conditions if other measures have failed and oral PUVA is felt less appropriate.

### **Indications for topical hand and foot psoralen ultraviolet A**

Topical PUVA has been extensively used and appears of value in the treatment of chronic hand and foot dermatoses, namely hyperkeratotic and dyshidrotic eczema, and hyperkeratotic and palmoplantar pustular psoriasis (PPP) (Table 1b).<sup>26–34</sup> However, randomized comparative studies of the efficacy of oral and topical PUVA are scarce. A retrospective review of 15 patients treated with oral 8-MOP and 25 with local immersion 8-MOP for chronic hand and foot dermatoses found the two modalities to be equally effective.<sup>26</sup> Using 8-MOP local immersion (1 mg/L), 93% (13 of 14) of patients with dyshidrotic eczema and 86% (12 of 14) of patients with hyperkeratotic eczema cleared or showed considerable improvement;<sup>27</sup> both the dyshidrotic and hyperkeratotic forms required a similar mean number

of treatments (12 and 15) and total UVA dose (21 and 28 J/cm<sup>2</sup>) for clearance.

Reports of the effect of PUVA in PPP are conflicting. In uncontrolled studies of topical 8-MOP PUVA, clearance has varied from 30% (three to 10) with local immersion or 0.1% ointment to 87% (13 of 15) with 0.15% emulsion.<sup>32,33</sup> In the latter study, similar response rates were found with topical and oral PUVA but maintenance treatment was noted to be required to prevent early relapse.<sup>33</sup> The clearance rate for oral 8-MOP PUVA in PPP has been reported as 86% (31 of 36) for palmar but only 15% (5 of 34) for plantar involvement.<sup>35</sup> However, a double-blind, placebo-controlled study of topical PUVA (0.75% 8-MOP emulsion, *n* = 27) for PPP, found similar improvements in both the treated and untreated groups.<sup>34</sup> In contrast to the findings in generalized plaque psoriasis, for palmar psoriasis local immersion with 5-MOP may be more effective than 8-MOP, when used in similar concentrations.<sup>7</sup> Moreover, in a comparative trial of oral and topical PUVA with etretinate, the etretinate was noted to be significantly more effective than either modality of PUVA.<sup>36</sup> Therefore, although local PUVA may be beneficial in other chronic hand and foot dermatoses, the case for recommending it in PPP is less convincing.

### **Indications for other forms of topical psoralen ultraviolet A**

There are a few reported studies of the use of other topical psoralen preparations such as paints, ointments and lotions (Table 1a), these having been applied principally in chronic hand and foot dermatoses (see previous section), but also sometimes used for the treatment of other sites. Disorders treated include vitiligo,<sup>37,38</sup> morphea,<sup>39</sup> mycosis fungoides,<sup>40</sup> atopic dermatitis<sup>41</sup> and uraemic pruritus.<sup>42</sup> Various products, concentrations and protocols are employed, and very little is known about their optimal use. Burning and patchy pigmentation can be a problem,<sup>43</sup> and the inadvertent spread of preparations on to unaffected skin can occur. Thus while they may provide a practical alternative to immersion psoralen for the treatment of localized disease, their use clearly demands greater medical supervision.

### **Use of adjunctive treatment**

It is anticipated that adjunctive treatments of benefit in oral PUVA might also increase the efficacy of bath PUVA, but currently no controlled trials of sufficient

power have been performed. However, six studies report the combination of topical PUVA regimens with oral retinoids (re-PUVA) to be beneficial in psoriasis, often with more rapid clearance and reduced total UVA dose.<sup>44–49</sup> Re-PUVA with either etretinate or acitretin appeared equally effective, and no differences were seen in relapse rates between topical 8-MOP alone or re-PUVA.<sup>46,47</sup> There are also isolated reports of the use of topical PUVA with anthralin,<sup>50</sup> and with tacalcitol,<sup>51</sup> and a single case report showing improvement of chronic actinic dermatitis with combined cyclosporin and bath PUVA therapy.<sup>52</sup>

## Adverse effects

### *Skin phototoxicity*

Comparative studies with oral 8-MOP PUVA have shown a far greater incidence of erythema or burning than with TMP baths<sup>8</sup> (40% vs. 16%) but roughly similar rates with bath 8-MOP.<sup>9–11</sup> In the past, difficulties with TMP solubility have led to unusual patterns of phototoxic burning due to the uneven distribution in the bath water.<sup>53</sup> It has also been stated that erythema is more protracted with bath than oral PUVA, lasting perhaps for 1 week even at threshold level.<sup>54,55</sup> Furthermore, increased sensitivity is reported to occur at about the fourth day of treatment, with the minimal phototoxic dose (MPD) decreasing by about 50%;<sup>9,56,57</sup> this may partly relate to the simple build-up of subclinical erythematous reactions due to the multiple PUVA treatments given per week in some studies. Additionally, it has been noted that a prolonged susceptibility to photosensitization can occur for up to 72 h after treatment (personal observation, J.Ferguson, Ninewells Hospital, Dundee, U.K.) despite the clearance of free drug from the skin.<sup>58</sup> A possible explanation for this might be that following the initial irradiation, psoralen DNA monoadducts occur which persist far longer in the skin than free psoralen, and with subsequent irradiation result in increased photosensitivity due to conversion to bifunctional adducts.<sup>59</sup> This is theoretical, however, and needs further study, and

until more information is available, it is recommended that photoprotective measures (i.e. adequate clothing, no sunbathing) are taken by patients both during the course and for up to a week after the course is completed.

### *Other acute effects*

Pruritus appears to be equally common following oral and bath PUVA, occurring in 10–40% of patients, but bath PUVA has the advantage that gastrointestinal symptoms such as nausea are avoided. Although rare, contact dermatitis and photocontact dermatitis have been reported with TMP and 8-MOP baths.<sup>5,60</sup>

### *Eye phototoxicity*

The current practice in the majority of units in the U.K. is not to recommend eye protection following bath PUVA. There is no published evidence of an increased incidence of cataract development in humans following oral or bath PUVA, and we can therefore only make an indirect judgement extrapolated from comparative information on plasma levels following oral and bath PUVA (Table 2). Both TMP and 8-MOP may be detected in plasma to variable degrees after topical administration,<sup>6,61–69</sup> but the concentrations of 8-MOP are generally very much lower than after oral dosing.<sup>64,65</sup> However, psoralen concentrations can be high with the application of paint/emulsion formulations to large areas, and comparable plasma levels with those with oral PUVA have been recorded for total body treatment with 0.15% 8-MOP emulsion;<sup>66</sup> on the other hand, such levels were found to be undetectable after 0.1% methoxsalen lotion to plaques covering less than 2% total surface area or to palmoplantar skin.<sup>67,68</sup> In contrast, TMP is poorly absorbed when given orally which explains why oral/bath concentrations are similar for this drug.<sup>6,62,63,70</sup> It has also been shown that psoriasis disease severity may influence psoralen absorption with greater plasma levels detected in patients with higher psoriasis area and severity index scores.<sup>69</sup> We therefore recommend that protective

**Table 2.** Comparison of plasma levels of 8-methoxypsoralen (8-MOP) and trimethylpsoralen (TMP) following oral and topical administration

No. of patients	Oral psoralen	Peak plasma levels (ng/mL)	Bath psoralen	Peak plasma levels (ng/mL)
4 oral, 8 bath <sup>64</sup>	8-MOP 0.5 mg/kg	108	8-MOP 1.87 mg/L	4.8
7 oral, 13 bath <sup>65</sup>	8-MOP 0.5 mg/kg	< 10–360	8-MOP 2.6 mg/L	< 10
21 oral, 5 bath <sup>62</sup>	TMP 30–40 mg	1.7–5.6	TMP 2.5 mg/L	2.3–15
11 oral <sup>61</sup>	TMP 30 mg	140–800	—	—
11 oral, 10 bath <sup>6</sup>	TMP 0.6 mg/kg	0.27–12.5	TMP 0.33 mg/L	0.025–9.0
2 oral, 6 bath <sup>63</sup>	TMP 40 mg	All less than sensitivity of method	TMP 0.33 mg/L	2.5

spectacles are advised on the day of treatment for patients with very extensive disease (i.e. > 30% surface area), in children, and in individuals with severe atopic eczema due to their increased lifetime risk.

### *Skin cancer*

The risk of non-melanoma skin cancer (NMSC) is now recognized following multiple treatments with oral PUVA, with an 11–13-fold relative risk of squamous cell carcinoma (SCC) and 3.7-fold relative risk of basal cell carcinoma (BCC) after more than 260 treatments.<sup>71</sup> No equivalent data exist for topical PUVA and there is currently insufficient evidence to conclude that this treatment is any safer.

*In vitro* work confirms the mutagenicity of TMP, 8-MOP and 5-MOP plus UVA, and in mice a dose relationship exists for SCC with both topical 8-MOP and 5-MOP plus UVA.<sup>72</sup> A melanocytic tumour has also been reported in one series of mice treated with topical PUVA.<sup>73</sup> Currently, there is insufficient evidence to reach a conclusion on the relative risk of topical and oral PUVA. In humans, studies to date have been limited by sample size and length of follow-up, with insufficient power to examine the long-term risk of NMSC associated with the use of topical PUVA.<sup>74,75</sup> It is generally held that the carcinogenic risk reflects the number of phototoxic episodes (i.e. the number of psoralen plus UVA treatments), rather than either the total UVA dose or the route of psoralen delivery. It is also likely that cancer risk is related to treatment efficacy; thus the lower cumulative UVA dose required for clearance with bath PUVA should not be interpreted as implying a lower carcinogenic risk, particularly as higher psoralen concentrations may be present in the skin thus making the overall effect of bath PUVA the same as for oral PUVA. While no excess risk of skin cancer has yet been reported in association with bath PUVA, keratoses and lentigines are common<sup>46</sup> and until there is good evidence to the contrary, it should probably be assumed that, for disease clearance, bath PUVA is as carcinogenic as oral PUVA. It is therefore recommended, as for oral PUVA, to keep bath PUVA treatments to a minimum.

## **Protocols for topical psoralen ultraviolet A**

### *Drug protocols*

It is evident from the preceding sections that many questions remain unanswered concerning the optimal protocols for topical PUVA. In the absence of studies to

address these issues, we recommend that the consensus current practice may be used for guidance. Most U.K. units use bath 8-MOP at a concentration of 2.6 mg/L (up to 3.7 mg/L), while the more phototoxic TMP is used at a concentration of 0.33 mg/L. A 15-min psoralen bath, given at a comfortably warm temperature, is then followed by immediate exposure to UVA (Appendix 2).

Some support for the above protocol is provided by diffusion theory and experimental permeability results. The lag time before a diffusing substance appears in appreciable quantity in the viable epidermis is a function of stratum corneum thickness and the diffusion coefficient. In excised normal skin *in vitro* the lag time for 8-MOP in aqueous solution at 32 °C for a stratum corneum thickness of 10 µm is 4 min, for 20 µm 15 min, and for 30 µm it would rise to 33 min.<sup>76</sup> However, diffusion will be influenced by factors such as vehicle characteristics<sup>77</sup> or the presence of emollients on the surface of the skin. Additionally, abnormalities of the stratum corneum as in psoriasis may lead to an increased permeability to psoralens when compared with unaffected skin. Further, while *in vitro* the penetration of normal epidermis by 8-MOP continues to rise in the 15–20 min after a 15-min bath,<sup>76</sup> MPDs *in vivo* appear to be similar for irradiation times from 0 to 20 min after bathing, prior to falling off significantly.<sup>78–81</sup> Using a 1% 8-MOP lotion the response to non-interval or 2 h interval PUVA on symmetrical plaques was found to be similar but with an increased risk of burning with delayed treatment.<sup>82</sup> Generally, the current practice of irradiating immediately after bathing therefore appears consistent with theory. In contrast, the lag time in palmoplantar skin is increased to 30–40 min,<sup>83</sup> implying that immediate irradiation of this site is inappropriate.

As differences in water temperature can alter the absorption kinetics of psoralens and thereby the MPD,<sup>84,85</sup> bath temperature should remain constant from treatment to treatment in order to reduce the risk of burning or undertreatment. A temperature of 37 °C appears optimal<sup>85</sup> and is comfortable for the patient. While a 15-min bathing time is generally given, it has been noted (personal observation, S.Thomas, Barnsley Hospital, U.K.) that there is no apparent loss in efficacy if the immersion time is reduced to 5 min. However, it is recommended that the 15-min bathing time is retained until further evidence is available.

In local immersion hand and foot PUVA, 8-MOP is generally used at a concentration of 3 mg/L (1.2% 8-MOP, 0.5 mL/2 L water) for a 15-min soak, and from

the above evidence we now recommend that a delay of at least 30 min is allowed before irradiation (Appendix 3). Preferences in preparations for the treatment of local disease vary widely depending on individual experience (Appendix 4), and where there are problems with 8-MOP emulsion, paint or gel formulations for hand and foot dermatoses, it is appropriate to change to the standard local immersion regimen.

#### *UVA protocols*

In PUVA generally, erythema is the limiting factor with regard to the UVA dose that can be given at each treatment, and therefore basic information on the MPD, dose–response characteristics and time-course is necessary to devise an efficient treatment regimen. A number of additional variables may affect the erythematous response in bath PUVA, including the type and formulation of psoralen, skin penetration, variation with body site, duration of bath and timing of irradiation. This may explain why the MPDs reported for bath 8-MOP<sup>9,55,86–88</sup> and TMP<sup>86,89</sup> show large variations, and why erythema is more problematic during courses of bath than oral PUVA, at least for TMP.<sup>8</sup> Comparative studies of bath TMP and 8-MOP PUVA confirm that in equivalent concentrations, TMP is up to 30 times more phototoxic.<sup>54,86</sup> Studies of bath 8-MOP PUVA in chronic plaque psoriasis usually report initial UVA doses of between 0.2 and 0.5 J/cm<sup>2</sup>, and while some studies use fixed dose increments, others report increments of 20–50% of the preceding dose, which are made every one to three visits.

In the absence of controlled trials to address optimal UVA-irradiation protocols for topical PUVA, the BPG makes recommendations based on the practice of its members (Appendices 2–4). In addition, in some areas it has been assumed that the same principles apply to bath PUVA as to oral PUVA. It is recommended first, that the initial UVA dose is based on an MPD test wherever possible, to avoid either painful erythema or, conversely, under-treatment. The determination of individual responses leads to a reduction in cumulative UVA dose and number of treatments in oral PUVA, and it is assumed that this will also occur in bath PUVA. The MPD test, defined as the lowest dose of UVA causing a perceptible erythema, should be performed on unexposed skin, and it is vital that the test site is fully immersed in psoralen prior to irradiation. Secondly, it is recommended that the initial UVA dose

should be 40–50% of the MPD, reflecting the greater tendency to burn compared with oral PUVA, where the initial dose is usually 70% of the MPD.<sup>1</sup> It is vital when transferring a patient from oral to bath PUVA to repeat the MPD test, in view of the generally lower UVA doses required. Thirdly, dose increments of 20–40% are recommended, with an increase every treatment. In vitiligo, however, it is appropriate to commence at a lower UVA dose of 0.1 J/cm<sup>2</sup>, and increase at fixed increments of 0.1 J/cm<sup>2</sup>, while higher UVA doses are recommended to treat the thicker skin of palmoplantar disorders.

#### **Practical and financial considerations**

Differences in the use of oral and topical PUVA necessitate the consideration of a number of practical issues. First, bathing facilities must be available and close nurse supervision is required throughout. The additional time taken for bathing may also reduce the throughput of patients, although this is somewhat countered by the reduction in irradiation times. The much lower exposure time required with bath PUVA can itself be problematic as there is a greater chance of error leading to accidental overtreatment, particularly if high-output machines are employed. Post-treatment bathing is unnecessary as cutaneous absorption and binding dynamics suggests that no free psoralen will remain on the skin surface, but of course exposed skin such as on the hands should still be protected from strong sunlight after local treatment.

A cost-effectiveness analysis of data collected across four centres during a Scottish phototherapy and PUVA audit in 1997 (personal communication, R.Dawe, Glasgow Western Infirmary, U.K.) revealed that courses of both bath and other topical PUVA were consistently more expensive than oral PUVA. This related predominantly to the increased nursing time required, although the greater cost of topical preparations was also a contributing factor.

#### **Conclusions**

Currently, oral PUVA is better established and studied than topical PUVA, and many questions remain concerning the efficacy, safety and optimal protocols of the latter. Thus, the carcinogenic risks of topical PUVA are unknown, and there is presently little firm evidence to suggest that the risk will be any lower than that of oral PUVA. However, advantages include shorter irradiation times and a lack of gastrointestinal and

systemic side-effects, and access of phototherapy units to facilities for both modalities is therefore desirable in order to permit a wider range of patients to be treated. Finally, as for oral PUVA, it is important that PUVA units have well trained staff to perform treatments, who should work closely with the dermatologist responsible for the prescribing and supervision of treatment.

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## Appendix 1: Psoralen formulations

All psoralens must currently be prescribed on a named patient basis, but the registration of oral 8-MOP is in progress (personal communication: M.Bedford-Stradling, Crawford Pharmaceuticals, U.K.). Topical formulations available from the main U.K. supplier (Crawford Pharmaceuticals, Milton Keynes, U.K.), include 8-MOP bath lotion (1.2%), emulsion (0.15%), paint (0.15%, 1.0%) and gel (0.005%), and TMP bath lotion (0.05%); the latter is also available from Tayside Pharmaceuticals (Dundee, U.K.). Other products which may be purchased from abroad include TMP bath lotion (50 mg/100 mL, Orion Pharmaceuticals Ltd., Espoo, Finland) and 0.75% 8-MOP paint (Promedica, Levallois-Perret, France).

## Appendix 2: Protocol for bath (generalized immersion) PUVA

### *Bath psoralen ultraviolet A with 8-methoxypsoralen*

- 1** Dissolve 30 mL of 1.2% 8-MOP lotion in 140 L water at 37 °C (final concentration 2.6 mg/L).
- 2** Bathe for 15 min, followed by immediate UVA exposure.
- 3** Initial UVA dose: either 40% of MPD (preferable) or 0.2–0.5 J/cm<sup>2</sup>.
- 4** UVA increments: increase by 20–40% of initial dose at each treatment.
- 5** Frequency: twice weekly.

### *Bath psoralen ultraviolet A with trimethylpsoralen*

- 1** Dissolve 50 mg TMP in 100 mL ethanol.
- 2** Mix in 150L water at 37 °C (final concentration 0.33 mg/L).
- 3** Bathe for 15 min, followed by immediate UVA exposure.
- 4** Initial UVA dose: either 40% of MPD (preferable) or 0.1–0.4 J/cm<sup>2</sup>.
- 5** UVA increments: increase by 0.5 of initial dose at each treatment.
- 6** Frequency: twice weekly.

## Appendix 3: Protocol for hand and foot immersion PUVA

### *8-methoxypsoralen lotion*

- 1** Mix 0.5 mL of 1.2% 8-MOP lotion in 2 L water (final concentration 3 mg/L).
- 2** Soak for 15 min, with a delay of 30 min before UVA exposure.
- 3** Initial UVA dose: 1–2 J/cm<sup>2</sup>.
- 4** UVA increments: 0.5–1 J/cm<sup>2</sup>.
- 5** Frequency: twice weekly.

### *Trimethylpsoralen lotion*

- 1** Dissolve 5 mg TMP in 10 mL ethanol.
- 2** Mix into 15 L water.
- 3** Soak for 15 min, with a delay of 30 min before UVA exposure.
- 4** Initial UVA dose: 1–2 J/cm<sup>2</sup>.
- 5** UVA increments: 0.5–1 J/cm<sup>2</sup>.
- 6** Frequency: twice weekly.

*Note:* If dorsa of hands or feet are affected give 50% of dose for palms and soles.

#### Appendix 4: Protocol for other topical 8-methoxypsoralen PUVA

##### *8-methoxypsoralen emulsion*

- 1** 0.15% (may be diluted 1 : 10 if erythema occurs at lowest UVA dose).
- 2** Apply 15 min before UVA exposure.
- 3** Initial UVA dose: either 40% of MPD, or (II) 0.5–1 J/cm<sup>2</sup> (depends on site).
- 4** UVA increments: 0.5–2 J/cm<sup>2</sup> (depends on site).
- 5** Frequency: twice weekly.

##### *8-methoxypsoralen gel*

- 1** 0.005% solution in aqueous gel.
- 2** Apply thin layer over diseased area using gloved hand.
- 3** Ensure repeated applications are given to same area.
- 4** Apply 15 min before UVA exposure.
- 5** Initial UVA dose: either 40% of MPD, or 0.5–1 J/cm<sup>2</sup> (depends on site).
- 6** UVA increments: 0.5–2 J/cm<sup>2</sup> (depends on site).
- 7** Frequency: twice weekly.