through healthy human skin after 24 hours was 0.26% of a dose and a skin depot containing 4.9% of the dose was formed.

◊ References.

1. Juzeniene A, *et al.* Topical application of 5-aminolaevulinic acid, methyl 5-aminolaevulinate and hexyl 5-aminolaevulinate on normal human skin. *Br J Dermatol* 2006; **155:** 791–9.

Uses and Administration

5-Aminolevulinic acid is a naturally occurring haem precursor that is metabolised in the body to protoporphyrin IX, a photosensitiser, and then to haem. It has been formulated for topical use in photodynamic therapy (see under Porfimer Sodium, p.764). It is used to treat actinic keratoses and basal cell carcinoma (see below). Aminolevulinic acid hydrochloride is applied topically as a 20% solution in the treatment of non-hyperkeratotic actinic keratoses of the face or scalp. This is followed, 14 to 18 hours later, by illumination with blue wavelength light sufficient to supply a dose of 10 J/cm^2. Treatment may be repeated once after 8 weeks if necessary.

Methyl aminolevulinate hydrochloride is a derivative of 5-aminolevulinic acid that is applied topically for the treatment of non-hyperkeratotic, non-pigmented actinic keratoses of the face or scalp when other therapies are considered inappropriate. It is also used for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for other therapies. In some countries, methyl aminolevulinate is licensed for the treatment of Bowen's disease (squamous cell carcinoma *in situ*) when surgical excision is inappropriate. A cream containing the equivalent of 16% methyl aminolevulinate is applied to the lesions and covered with an occlusive dressing. After 3 hours the cream is removed and the lesions are exposed to red wavelength light in a dose of 75 J/cm^2; exposure to the cream for more than 4 hours should be avoided. For actinic keratoses, one session of photodynamic therapy is given, and again after 3 months if necessary. For basal cell carcinoma or Bowen's disease two sessions are given a week apart.

Patients should avoid sunlight or bright light sources for about 2 days after application.

Hexaminolevulinate hydrochloride is used as a diagnostic agent for the detection of bladder cancer (p.659), and is under investigation for the photodynamic therapy of bladder cancer.

Malignant neoplasms. The use of topical aminolevulinic acid or methyl aminolevulinate in the photodynamic therapy (PDT) of *actinic keratosis* and *basal cell carcinoma* (p.673) has been reviewed.[1-5] Both aminolevulinic acid and methyl aminolevulinate are considered to be effective in clearing non-hyperkeratotic actinic keratoses of the face and scalp, with response rates comparable to topical 5-fluorouracil and cryotherapy; cosmetic response is superior to that with cryotherapy.[6,7] More than 80% of lesions cleared completely after 2 treatments with aminolevulinic acid PDT; a recurrence rate of 19% was reported over 12 months.[8] Single treatment with methyl aminolevulinate is effective for thin lesions but thicker, non-responsive lesions may benefit from repeated treatment.[9] No significant differences in efficacy were seen between PDT with aminolevulinic acid or methyl aminolevulinate in the treatment of scalp actinic keratosis.[10] Aminolevulinic acid is considered as effective as cryotherapy but with superior healing and cosmetic results for superficial basal cell carcinoma; it is less effective for nodular disease.[6] Intralesional use has been investigated to improve penetration of the photosensitiser, with good preliminary results.[11] Methyl aminolevulinate topical PDT may be preferable for difficult-to-treat basal cell carcinoma.[12,13] Aminolevulinic acid is as effective in *Bowen's disease* (squamous cell carcinoma *in situ*) as cryotherapy or 5-fluorouracil, but with fewer adverse effects.[6] Topical methyl aminolevulinate PDT was more effective and cosmetically acceptable compared with topical 5-fluorouracil for pre-malignant skin disease in a small study in organ transplant recipients.[14]

PDT using oral 5-aminolevulinic acid as the photosensitiser, at doses of 30 or 60 mg/kg, has been used to treat *Barrett's oesophagus*, which is a major risk factor for oesophageal adenocarcinoma (p.664).[15,16] A small study found similar clinical responses with low-dose (30 mg/kg) and high-dose (60 mg/kg) aminolevulinic acid protocols.[17] Good long-term results have been reported with aminolevulinic acid PDT in patients with early neoplasia or high-grade intraepithelial neoplasia.[18]

Aminolevulinic acid is also under investigation for the photodynamic detection and treatment of *brain tumours* (p.660).[19] It has also been used for the fluorescence detection of *pleural malignancies*.[20]

An intravesical solution of aminolevulinic acid has been instilled for the detection[21] and management[22] of superficial *bladder cancer* (p.659). Hexaminolevulinate is used for the diagnosis of bladder cancer, and it appears to be more effective than standard white light cystoscopy.[23-25]

A topical application of 5-aminolevulinic acid 3% has been tried in the treatment of *cervical intraepithelial neoplasia*, with poor response.[26]

1. Ormrod D, Jarvis B. Topical aminolevulinic acid HCl photodynamic therapy. *Am J Clin Dermatol* 2000; **1:** 133–9.
2. Gupta AK, Ryder JE. Photodynamic therapy and topical aminolevulinic acid: an overview. *Am J Clin Dermatol* 2003; **4:** 699–708.
3. Siddiqui MAA, *et al.* Topical methyl aminolevulinate. *Am J Clin Dermatol* 2004; **5:** 127–37.
4. Marmur ES, *et al.* A review of laser and photodynamic therapy for the treatment of nonmelanoma skin cancer. *Dermatol Surg* 2004; **30:** 264–71.
5. Lehmann P. Methyl aminolaevulinate-photodynamic therapy: a review of clinical trials in the treatment of actinic keratoses and nonmelanoma skin cancer. *Br J Dermatol* 2007; **156:** 793–801.
6. Morton CA, *et al.* Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2002; **146:** 552–67.
Also available at: http://www.bad.org.uk/healthcare/guidelines/topical_photodynamic_therapy.pdf (accessed 09/05/08)
7. Morton C, *et al.* AKtion Investigators. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155:** 1029–36.
8. Tschen EH, *et al.* Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155:** 1262–9.
9. Tarstedt M, *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; **85:** 424–8.
10. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol* 2007; **157:** 87–91.
11. Cappugi P, *et al.* New proposal for the treatment of nodular basal cell carcinoma with intralesional 5-aminolevulinic acid. *J Chemother* 2004; **16:** 491–3.
12. Horn M, *et al.* Topical methyl aminolaevulinate photodynamic therapy in patients with basal cell carcinoma prone to complications and poor cosmetic outcome with conventional treatment. *Br J Dermatol* 2003; **149:** 1242–9.
13. Vinciullo C, *et al.* Photodynamic therapy with topical methyl aminolaevulinate for 'difficult-to-treat' basal cell carcinoma. *Br J Dermatol* 2005; **152:** 765–72.
14. Perrett CM, *et al.* Treatment of post-transplant premalignant skin disease: a randomized intrapatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol* 2007; **156:** 320–8.
15. Ackroyd R, *et al.* Photodynamic therapy for dysplastic Barrett's oesophagus: a prospective, double blind, randomised, placebo controlled trial. *Gut* 2000; **47:** 612–17.
16. Barr H. Barrett's esophagus: treatment with 5-aminolevulinic acid photodynamic therapy. *Gastrointest Endosc Clin N Am* 2000; **10:** 421–37.
17. Kelty CJ, *et al.* Comparison of high- vs low-dose 5-aminolevulinic acid for photodynamic therapy of Barrett's esophagus. *Surg Endosc* 2004; **18:** 452–8.
18. Pech O, *et al.* Long-term results of photodynamic therapy with 5-aminolevulinic acid for superficial Barrett's cancer and high-grade intraepithelial neoplasia. *Gastrointest Endosc* 2005; **62:** 24–30.
19. Friesen SA, *et al.* 5-Aminolevulinic acid-based photodynamic detection and therapy of brain tumors (review). *Int J Oncol* 2002; **21:** 577–82.
20. Baas P, *et al.* Fluorescence detection of pleural malignancies using 5-aminolaevulinic acid. *Chest* 2006; **129:** 718–24.
21. Zaak D, *et al.* Role of 5-aminolevulinic acid in the detection of urothelial premalignant lesions. *Cancer* 2002; **95:** 1234–8. Correction. *ibid.*; 2580.
22. Kriegmair M, *et al.* Early clinical experience with 5-aminolevulinic acid for the photodynamic therapy of superficial bladder cancer. *Br J Urol* 1996; **77:** 667–71.
23. Anonymous. Hexyl aminolevulinate: 5-ALA hexylester, 5-ALA hexylesther, aminolevulinic acid hexyl ester, hexaminolevulinate, hexyl-5-aminolevulinate, P 1206. *Drugs R D* 2005; **6:** 235–8.
24. Jocham D, *et al.* Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. *J Urol (Baltimore)* 2005; **174:** 862–6.
25. Frampton JE, Plosker GL. Hexyl aminolevulinate: in the detection of bladder cancer. *Drugs* 2006; **66:** 571–8.
26. Barnett AA, *et al.* A randomised, double-blind, placebo-controlled trial of photodynamic therapy using 5-aminolaevulinic acid for the treatment of cervical intraepithelial neoplasia. *Int J Cancer* 2003; **103:** 829–32.

Skin disorders. 5-Aminolevulinic acid has been used topically in the photodynamic therapy (PDT) of skin conditions such as psoriasis, recalcitrant viral warts, acne vulgaris, and cutaneous T-cell lymphoma.[1] Variable results have been reported with this therapy in patients with plaque psoriasis; in one study therapy was generally well-tolerated,[2] but in the other all patients reported stinging or burning during irradiation.[3] A study comparing 5-aminolevulinic acid and methyl aminolevulinate for PDT of acne found both to be equally effective, although methyl aminolevulinate seemed to be better tolerated.[4] Topical methyl aminolevulinate-based PDT has been found to be effective in the treatment of facial acne vulgaris.[5,6] PDT with 5-aminolevulinic acid has been reported to significantly improve an infected leg ulcer resistant to conventional therapies.[7] A topical 10% solution has been used with intraurethral PDT to treat condylomata acuminata.[8]

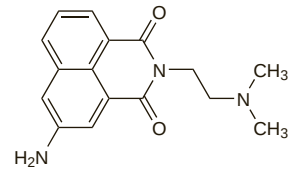
1. Ibbotson SH. Topical 5-aminolaevulinic acid photodynamic therapy for the treatment of skin conditions other than nonmelanoma skin cancer. *Br J Dermatol* 2002; **146:** 178–88.
2. Smits T, *et al.* A placebo-controlled randomized study on the clinical effectiveness, immunohistochemical changes and protoporphyrin IX accumulation in fractionated 5-aminolaevulinic acid-photodynamic therapy in patients with psoriasis. *Br J Dermatol* 2006; **155:** 429–36.
3. Radakovic-Fijan S, *et al.* Topical aminolaevulinic acid-based photodynamic therapy as a treatment option for psoriasis? Results of a randomized, observer-blinded study. *Br J Dermatol* 2005; **152:** 279–83.
4. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using 5-aminolevulinic acid versus methyl aminolevulinate. *J Am Acad Dermatol* 2006; **54:** 647–51.
5. Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolaevulinate: a blinded, randomized, controlled trial. *Br J Dermatol* 2006; **154:** 969–76.
6. Hörfelt C, *et al.* Topical methyl aminolaevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol* 2006; **155:** 608–13.
7. Clayton TH, Harrison PV. Photodynamic therapy for infected leg ulcers. *Br J Dermatol* 2007; **156:** 384–5.
8. Wang XL, *et al.* Topical 5-aminolaevulinic acid-photodynamic therapy for the treatment of urethral condylomata acuminata. *Br J Dermatol* 2004; **151:** 880–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Metvix; ***Belg.:*** Metvix; ***Cz.:*** Hexvix; MC 506; Metvix; ***Denm.:*** Metvix; ***Fin.:*** Hexvix; Metvix; ***Fr.:*** Metvixia; ***Ger.:*** Metvix; ***Gr.:*** Hexvix; ***Ital.:*** Metvix; ***Neth.:*** Hexvix; Metvix; ***Norw.:*** Hexvix; Metvix; ***NZ:*** Metvix; ***Port.:*** Gliolan; Hexvix; Metvix; ***S.Afr.:*** Metvix; ***Spain:*** Metvix; ***Swed.:*** Hexvix; Metvix; ***Switz.:*** Metvix; ***UK:*** Metvix; Porphin; ***USA:*** Levulan Kerastick; Metvixia.

Amonafide *(rINN)*

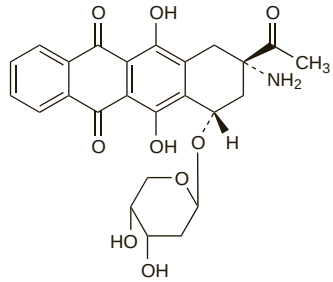
Amonafida; Amonafidum; M-FA-142; Nafidimide; NSC-308847.
3-Amino-*N*-[2-(dimethylamino)ethyl]naphthalimide.
Амонафид
$C_{16}H_{17}N_3O_2$ = 283.3.
CAS — 69408-81-7.



Profile
Amonafide is a topoisomerase inhibitor. Amonafide malate is under investigation for the treatment of acute myeloid leukaemia. Amonafide hydrochloride has also been investigated, but studies were stopped due to serious adverse effects.

Amrubicin *(USAN, rINN)*

Amrubicina; Amrubicine; Amrubicinum; SM-5887. (+)-(7*S*,9*S*)-9-Acetyl-9-amino-7-[(2-deoxy-β-D-*erythro*-pentopyranosyl)-oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione.
Амрубицин
$C_{25}H_{25}NO_9$ = 483.5.
CAS — 110267-81-7 (amrubicin); 110311-30-3 (amrubicin hydrochloride).



Profile
Amrubicin is a synthetic anthracycline derivative related to compounds such as doxorubicin (p.712). Amrubicin hydrochloride is used as an antineoplastic in the treatment of lung cancer, and is under investigation in the treatment of superficial bladder cancers, and lymphomas.