WHO/DMP/DSI/98.1
Original: English
Distribution: General

WHO Model Prescribing Information

Drugs Used in Leprosy

World Health Organization
Geneva
1998

CONTENTS

PREFACE

The Revised Drug Strategy of the World Health Organization adopted in World Health Assembly Resolution WHA39.27 and revised in Resolution WHA49.14 in May 1996, calls for the preparation of model prescribing information to complement the WHO Model List of Essential Drugs. This will provide source material for adaptation by national authorities - particularly in developing countries - wishing to develop national drug formularies, drug compendia and similar material.

This information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug appropriate to circumstances prevailing in each of WHO's Member States. Also, some countries have already formally adopted texts of their own that have a statutory connotation.

This WHO Model Prescribing Information was written by the Division of Drug Management and Policies with the cooperation of the Action Programme for the Elimination of Leprosy, WHO, Geneva. It describes the WHO currently recommended drugs, doses and dosage regimens for leprosy.

INTRODUCTION

Leprosy is a chronic mycobacterial infection that affects about 1.15 million people, mainly in Brazil, India, Indonesia, Myanmar and Nigeria. This significant reduction on the 10-12 million people affected 12 years ago follows the introduction of multidrug therapy (MDT).The World Health Organization and its Member States are working to eliminate leprosy as a public health problem throughout the world by the end of year 2000, i.e., to reduce the prevalence to less than one case per 10 000 population.

Leprosy is an infectious disease caused by *Mycobacterium leprae,* which is a slow-growing intracellular bacillus that infiltrates the skin, the peripheral nerves, the nasal and other mucosa, and the eyes. The incubation period between infection and appearance of leprosy is normally between two and 10 years but may be as long as 20 years. Leprosy can affect all ages and both sexes.

Humans infected with leprosy are the primary reservoir. Close and prolonged contact within the household is a significant factor in the transmission of disease. Leprosy infection probably occurs when leprosy bacteria are discharged through the nose. Leprosy is transmitted to a previously uninfected person when nasal secretions from a *M. leprae* infected leprosy patient contaminate the nasal mucosa or minor skin abrasions of the previously uninfected person. However, most individuals have considerable natural immunity and many infections are suppressed. Leprosy cases seldom develop in non-endemic areas without known close contacts.

The main clinical features of leprosy are a variety of skin lesions and peripheral nerve trunk damage, which lead to anaesthesia and paralysis causing the trophic changes and deformities which are characteristic of leprosy.

Neuropathy in leprosy affects the small dermal nerves and peripheral nerve trunks. Nerve damage occurs in untreated leprosy patients and also those on chemotherapy and when treatment is withdrawn as a result of neuritis associated with reversal and erythema nodosum leprosum (ENL) reactions.

Visual impairment or blindness is a frequent complication of leprosy. Blindness results either from mycobacterial infiltration and inflammation of structures in the anterior segment of the eye or from trophic changes following damage to the trigeminal and facial nerves, resulting in lagophthalmos, deformed eyelids or corneal anaesthesia.

Diagnosis of leprosy

Many procedures for the diagnosis of leprosy have been simplified so that leprosy patients can be detected by general health workers in the field. The experience gained from many endemic countries demonstrates that, after appropriate training, health workers at the peripheral level are able to diagnose and treat leprosy. Currently, the diagnosis of leprosy is based on clinical signs and symptoms.

In an endemic country or area, an individual should be regarded as having leprosy if he or she has one of the following features:

> *hypopigmented or reddish skin lesion(s) with definite loss of sensation;*
> *involvement of the peripheral nerves, as demonstrated by loss of sensation and weakness of the muscles of hands, feet or face;*
> *skin smear positive for acid-fast bacilli.*

The skin lesion can be single or multiple, usually less pigmented than the surrounding normal skin. Sometimes the lesion is reddish or copper-coloured. A variety of skin lesions may be seen but macules, papules or nodules are common. Sensory loss is a typical feature of leprosy. The skin lesion may show loss of sensation to pin prick and/or light touch.

Nerve damage, mainly to peripheral nerve trunks, constitutes another feature of leprosy. This may be manifested by loss of sensation in the skin and weakness of muscles supplied by the affected nerve. In the absence of these signs, nerve thickening by itself without sensory loss and/or muscle weakness is often not a reliable sign of leprosy.

Positive skin smears: In a small proportion of cases, rod-shaped, red-stained leprosy bacilli, which are diagnostic of the disease, may be seen in the smears taken from the affected skin when examined under a microscope after appropriate staining.

Household contacts of leprosy patients are at significantly greater risk of developing leprosy than contacts who are not living in the same household. When a new case is detected, his or her household contacts should be examined for evidence of leprosy. They should be taught to recognize the early signs of leprosy and be taught to understand the significance of the early signs. They should also be told to return to the health care centre if any suspect skin lesion or signs or symptoms of nerve damage occur.

Classification of leprosy

For treatment purposes patients can be divided into three groups: paucibacillary single-lesion leprosy, paucibacillary leprosy and multibacillary leprosy. Skin smears were originally used to distinguish between paucibacillary and multibacillary leprosy. However, because services for processing skin smears are not always available, and also because their reliability is often doubtful, in practice most leprosy programmes classify and choose the appropriate regimen for a particular patient using clinical criteria, which uses the number of skin lesions and nerves involved to classify leprosy patients into paucibacillary single-lesion leprosy (one skin lesion), paucibacillary leprosy (2–5 skin lesions) and multibacillary leprosy (more than five skin lesions).

When skin smears are available and are dependable, any patient with a positive skin smear, irrespective of the clinical picture, must be classified

as multibacillary leprosy and must be treated with the multidrug therapy regimen for multibacillary leprosy.

Treatment of leprosy

Several drugs are used in combination in multidrug therapy (MDT). (See table) These drugs must never be used alone as monotherapy for leprosy.

Dapsone, which is bacteriostatic or weakly bactericidal against *M. leprae*, was the mainstay treatment for leprosy for many years until widespread resistant strains appeared. Combination therapy has become essential to slow or prevent the development of resistance. **Rifampicin** is now combined with **dapsone** to treat paucibacillary leprosy. **Rifampicin** and **clofazimine** are now combined with **dapsone** to treat multibacillary leprosy.

A single dose of combination therapy has been used to cure single lesion paucibacillary leprosy: **rifampicin** (600 mg), **ofloxacin** (400 mg), and **minocycline** (100 mg). The child with a single lesion takes half the adult dose of the 3 medications.

WHO has designed blister pack medication kits for both paucibacillary leprosy and for multibacillary leprosy. Each easy-to use kit contains medication for 28 days. The blister pack medication kit for single lesion paucibacillary leprosy contains the necessary medication for the one time administration of the 3 medications.

Any patient with a positive skin smear must be treated with the MDT regimen for multibacillary leprosy. The regimen for paucibacillary leprosy should never be given to a patient with multibacillary leprosy. Therefore, if the diagnosis in a particular patient is uncertain, treat that patient with the MDT regimen for multibacillary leprosy.

Ideally, the patient should go to the leprosy clinic once a month so that clinic personnel may supervise administration of the drugs prescribed

once a month. However, many countries with leprosy have poor coverage of health services and monthly supervision of drug administration by health care workers may not be possible. In these cases, it may be necessary to designate a responsible third party, such as a family member or a person in the community, to supervise the monthly drug administration. Where health care service coverage is poor and supervision of the monthly administration of drugs by health workers is not possible, the patient may be given more than the 28 days supply of multidrug therapy blister packs. This tactic helps make multidrug therapy easily available, even to those patients who live under difficult conditions or in remote areas. Patients who ask for diagnosis and treatment are often sufficiently motivated to take full responsibility for their own treatment of leprosy. In this situation, it is important to educate the patient regarding the importance of compliance with the regimen and to give the patient responsibility for taking his or her medication correctly and for reporting any untoward signs and symptoms promptly. The patient should be warned about possible lepra reactions.

WHO Recommended treatment regimens

6 month regimen for Paucibacillary (PB) Leprosy

	Dapsone	**Rifampicin**
Adult 50-70 kg	100 mg Given daily	600 mg Given once a month under supervision
Child 10-14 years [a]	50 mg Given daily	450 mg Given once a month under supervision

[a] Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily and rifampicin 300 mg given once a month under supervision

12 month regimen for Multibacillary (MB) Leprosy

	Dapsone	**Rifampicin**	**Clofazimine**
Adult 50-70 kg	100 mg Given daily	600 mg Given once a month under supervision	50 mg AND 300 mg Given daily Given once a month under supervision
Child 10-14 years [b]	50 mg Given daily	450 mg Given once a month under supervision	50 mg AND 150 mg Given every other day Given once a month under supervision

[b] Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily, rifampicin 300 mg given once a month under supervision, clofazimine, 50 mg given twice a week, and clofazimine 100 mg given once a month under supervision

Single Lesion Paucibacillary (SLPB) Leprosy
(one time dose of 3 medications taken together)

	Rifampicin	Ofloxacin	Minocycline
Adult 50–70 kg	600 mg	400 mg	100 mg
Child 5–14 years [c]	300 mg	200 mg	50 mg

[c] Not recommended for pregnant women or children less than 5 years

Treatment of lepra reactions

During the course of leprosy, immunologically mediated episodes of acute or subacute inflammation known as reactions may occur in up to 25% of patients with paucibacillary leprosy and as much as 40% in multibacillary leprosy. Clinical indications of a reaction are nerve pain, loss of sensation and loss of function. The reactions may rapidly cause severe and irreversible nerve damage and must always be treated promptly. If a patient does not respond to lepra reaction treatment within 4 weeks or his/her condition deteriorates at any time during lepra reaction treatment, send that patient immediately to the nearest specialist centre. During a lepra reaction, do not interrupt leprosy multidrug therapy. Treatment with multidrug therapy reduces the frequency and severity of lepra reactions.

Type 1 lepra reactions or reversal reactions are associated with the development of *M. leprae* antigenic determinants. They are delayed hypersensitivity reactions and may occur in both paucibacillary leprosy and multibacillary leprosy. In type 1 lepra reactions, there is a high risk of permanent damage to the peripheral nerve trunks. If the reaction is mild and there is no evidence of neuritis (pain, loss of sensation or

function), the reaction should be treated with analgesics, such as acetylsalicylic acid or paracetamol. However, if there is nerve involvement, treat type 1 reactions with analgesics and corticosteroids, such as oral prednisolone. The usual course begins with 40–60 mg daily (up to a maximum of 1 mg/kg), and the reaction is generally controlled within a few days. The dose is then gradually reduced weekly or fortnightly and eventually stopped. Most reversal reactions and neuritis can be treated successfully under field conditions with a standard 12-week course of prednisolone but some authorities claim that corticosteroids need to be continued for much longer periods of time.

Type 2 lepra reactions (erythema nodosum leprosum), are associated with circulation and tissue deposition of immune complexes. They are an antibody response or immune complex response to *M. leprae* antigenic determinants which occur only in multibacillary leprosy. Therapy for type 2 reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and corticosteroids, such as oral prednisolone.

In patients with severe type 2 reactions, who do not respond to corticosteroids or in whom corticosteroids are contraindicated, clofazimine at high doses or thalidomide may be used under close medical supervision. Clofazimine often requires 4–6 weeks before an effect is seen, and therefore must never be used as the sole drug for treatment of severe type 2 reactions. However, it may be useful for reducing or withdrawing corticosteroids from patients who have become dependent on corticosteroids. The clofazimine dose for treatment of severe type 2 reactions is 300 mg daily, which should be given in 3 doses of 100 mg each. The total duration of this high dose of clofazimine should not exceed 12 months. Thalidomide should be avoided in women of childbearing age since it is a proven teratogen. If this is not possible, it is imperative that pregnancy is excluded before this treatment is initiated. Effective contraception must be used during the 4 weeks preceding and following treatment as well as during the treatment period. Should pregnancy occur despite these precautions, there is a high risk of severe malformation of the fetus.

Treatment of neuritis

Neuritis may occur during lepra reactions or may occur independent of lepra reactions. Neuritis is an acute inflammation of the nerves with nerve pain, local oedema and rapid loss of function. Neuritis may occur before leprosy is diagnosed, during leprosy treatment, or up to several years after leprosy treatment has been completed. All neuritis of less than 6 months duration should be treated with the standard 12 week regimen of oral prednisolone. The usual course of oral prednisolone treatment begins with 40–60 mg daily up to a maximum of 1 mg/kg body weight per day and normally controls the neuritis within a few days. Most neuritis can be treated successfully under field conditions with the standard 12 week oral prednisolone treatment. If patients with neuritis do not respond to corticosteroid therapy, they should be sent to the specialist centre.

Treatment of eye complications

The eye is particularly vulnerable in leprosy. In the absence of adequate care, damage to the eye occurs in a significant number of leprosy patients. Loss of vision is often preventable and the eyes should be examined regularly in all leprosy patients. The eye may be damaged by direct bacillary invasion or by nerve damage. Leprosy patients may develop ocular complications, such as corneal ulceration, or iridocyclitis (inflammation of the iris and ciliary body). Corneal ulceration may result from corneal anaesthesia or from paralysis of the eyelids. Recurrent attacks of iridocyclitis may cause glaucoma or cataracts.

When the patient cannot close the eye lids properly (lagophthalmos) and the episode is acute or recent (less than 6 months), treat the patient with a course of the standard 12 week course of oral prednisolone. At night, the patient should wear an eye patch or an eye mask that covers both eyes to prevent airborne dirt and dust from irritating the eyes.

Paralysis of the eyelids may lead to corneal ulceration and tarsorrhaphy may be required. Iridocyclitis causes pain, redness and watering in the

eyes and photophobia. In the absence of corneal ulcers, iridocyclitis should be treated with topical corticosteroids (prednisolone 0.5%) applied 4 to 6 times daily and with daily instillations of atropine 1% to dilate the pupil and relax the ciliary muscle until the attack subsides. Corticosteroid application should be gradually reduced in frequency over a week before the corticosteroid is finally withdrawn. Mydriatics should similarly be administered 2 or 3 times weekly for 2–4 weeks after the initial attack has subsided. Corticosteroids reduce resistance to infections particularly trachoma, herpes and other viruses. If coincidental infection is suspected, give a mydriatic together with an antibiotic for the infection for 2 days before introducing topical corticosteroids.

Corneal abrasions, must be treated as soon as possible with an antibiotic eye ointment (tetracycline 1 %). Several applications daily may be needed for a prolonged period of time. The eye should be covered at all times with an eye mask and should remain covered until the lesion heals. If the patient has a corneal ulcer, apply antibiotic eye ointment, cover the eye, and refer the patient immediately to a specialist. Similarly, if the patient has sudden changes in visual acuity, refer the patient immediately to a specialist.

Management of nerve damage

Nerve damage produces anaesthesia, dryness and muscle weakness. These three factors lead to misuse of the affected limb, with resultant ulceration, infection and ultimately, severe deformity. Dryness of the skin leads to skin cracking and secondary infection. Patients should soak their feet and hands in water and apply petroleum jelly (vaseline) on their hands and feet.

If the patient has a shallow or deep plantar ulcer without any discharge, clean the ulcer with soap and water. Cover with a non-bulky clean dressing. If the patient has a deep ulcer or if no improvement occurs within 4 weeks, refer the patient to a specialist.

Treatment of leprosy during pregnancy and lactation

Leprosy is exacerbated during pregnancy, so it is important that the standard multidrug therapy be continued during pregnancy. The Action Programme for the Elimination of Leprosy, WHO, Geneva has stated that the standard MDT regimens are considered safe, both for the mother and the child, and therefore, should be continued unchanged during pregnancy. A small quantity of antileprosy drugs is excreted through breast milk but there is no report of adverse effects as a result of this except for mild skin discolouration of the infant due to clofazimine. The single dose treatment for patients with single lesion paucibacillary leprosy should be deferred until after delivery.

Treatment of patient with concomitant active tuberculosis

If the patient has both leprosy and active tuberculosis, it is necessary to treat both infections at the same time. Give the appropriate antituberculosis therapy, in addition to the antileprosy multidrug therapy for the type of leprosy in the patient. Rifampicin is common to both regimens and it must be given in the doses required for tuberculosis.

Treatment of patients with concomitant HIV infection

The management of a leprosy patient infected with HIV is the same as that of any other patient. The information available so far indicates that the response of such a patient to MDT is similar to that of any other leprosy patient and management, including treatment of reactions, does not require any modifications.

Treatment of leprosy in special situations

Patient who cannot take rifampicin

Special treatment regimens are required for individual patients, who cannot take rifampicin because of allergy or intercurrent diseases, such

as chronic hepatitis, or who have been infected with rifampicin-resistant leprosy.

In 1997, the WHO Expert Committee on Leprosy recommended the following 24 month regimen for adult patients with multibacillary leprosy, who cannot take rifampicin:

Length of Treatment	Drug	Dose
6 months	clofazimine	50 mg daily
	ofloxacin	400 mg daily
	minocycline	100 mg daily
Followed by an additional		
18 months	clofazimine	50 mg daily
	plus either	
	ofloxacin	400 mg daily
	or	
	minocycline	100 mg daily

In 1994, the WHO Study Group on Chemotherapy of Leprosy stated that daily administration of 500 mg of clarithromycin can be substituted in the above regimen for either ofloxacin or minocycline during the first six months of treatment of multibacillary patients, who cannot take rifampicin.

Patient who refuses to take clofazimine

Patients with multibacillary leprosy, who refuse to take clofazimine because of skin discolouration, also need a safe and effective alternative treatment. In such patients, clofazimine in the normal 12 month multidrug therapy may be replaced by:

- ofloxacin, 400 mg daily for 12 months OR
- minocycline, 100 mg daily for 12 months

In 1997, the WHO Expert Committee on Leprosy also recommended the following alternative 24 month multidrug therapy regimen (3 drugs) for adult patients with multibacillary leprosy, who refuse to take clofazimine:

- rifampicin, 600 mg once a month for 24 months,
- ofloxacin, 400 mg once a month for 24 months, AND
- minocycline, 100 mg once a month for 24 months

Patient who cannot take dapsone:

If dapsone produces severe toxic effects in any leprosy patient, either with paucibacillary or multibacillary leprosy, dapsone must be immediately stopped. No further modification of the regimen is required for patients with multibacillary leprosy. However, clofazimine in the dosage employed in the standard multidrug therapy for multibacillary leprosy should be substituted for dapsone in the regimen for paucibacillary leprosy for a period of 6 months. Thus, the MDT 6 month regimen for patients with paucibacillary (PB) leprosy, who cannot take dapsone, would be:

	Rifampicin	Clofazimine	
Adult 50-70 kg	600 mg Given once a month under supervision	50 mg *and* Given daily	300 mg Given once a month under supervision
Child 10-14 years	450 mg Given once a month under supervision	50 mg *and* Given every other day	150 mg Given once a month under supervision

Other special situations

After completing the multidrug therapy regimen for leprosy, patients may have a lepra reaction (either Type 1 or Type 2) or may develop neuritis.

These patients should be treated with oral prednisolone as if they had developed lepra reactions during MDT. There is a small risk of relapse in these patients since corticosteroids are known to accelerate the multiplication of organisms located in dormant foci and may cause disseminated reactivation. Thus, it is recommended that clofazimine, 50 mg daily, should be given as a prophylactic measure if the duration of corticosteroid therapy is expected to exceed 4 months. Clofazimine should be continued until corticosteroid therapy is stopped.

Further information regarding leprosy can be obtained from the Action Programme for the Elimination of Leprosy, World Health Organization, Geneva, Switzerland.

See also the following publications:

1. *WHO Expert Committee on Leprosy. Seventh Report*, Geneva, World Health Organization, 1998, (WHO Technical Report Series No. 874).

2. A *Guide to Eliminating Leprosy as a Public Health Problem, Second Edition*, 1997, WHO/LEP/97.7

3. Single Lesion Multicentre Trial Group, Efficacy of Single Dose Multidrug Therapy for Treatment of Single Lesion Paucibacillary Leprosy, 1997, *Indian Journal of Leprosy*, 69, 121-129.

4. MDT, Questions and Answers, Revised 1997, WHO/LEP/97.8

5. Chemotherapy of Leprosy, Report of a WHO Study Group, Geneva, World Health Organization, 1994 (WHO Technical Report Series No. 847).

6. Courtright, Paul and Johnson, Gordon J.(editors), Prevention of Blindness in Leprosy, Revised Edition, The International Centre for Eye Health, 27-29 Cayton Street, London EC1V 9EJ, England, 1991

CLOFAZIMINE

Group: antimycobacterial agent
Capsule 50 mg, 100 mg

General information

A substance with both antileprosy and anti-inflammatory activity. It is weakly bactericidal against *M. leprae* and antimicrobial activity can be demonstrated in humans only after continuous exposure for about 50 days. When taken orally it is well absorbed and intermittent dosage is effective because the drug accumulates in fatty tissues and the cells of the reticuloendothelial system. It is very slowly eliminated in the faeces with a half-life of abut 70 days. As yet, resistance to clofazimine is rare.

Clinical information

Uses: Multibacillary leprosy in combination with dapsone and rifampicin. For Type 2 lepra reactions as an alternative or in addition to analgesics, corticosteroids or thalidomide

Dosage:

Multibacillary leprosy (in combination with dapsone and rifampicin)
Adults: 50 mg daily for 12 months, AND once a month, a dose of 300 mg, supervised.
Children (10–14 years): 50 mg given on alternate days for 12 months, AND once a month, a dose of 150 mg, supervised.
Children, less than 10 years: Adjust the dose. For example, Clofazimine, 50 mg twice a week for 12 months AND once a month, a dose of 100 mg, supervised.
Erythema nodosum leprosum (Type 2 lepra reactions)
Adults and children: 200-300 mg daily in 2 or 3 divided doses. 4–6 weeks may be needed before an effect is seen. Hospitalize a patient with severe Type 2 lepra reactions for supervised medical care.

Precautions: Patients with pre-existing gastrointestinal disease and hepatic disease should be kept under medical supervision. If symptoms become severe, it may be necessary to reduce the dosage or to prolong the interval between doses. Liver function and creatinine clearance should be monitored.

Adverse effects: Reversible skin discolouration may occur during treatment to an extent that some lighter-skinned patients find unacceptable.
Discolouration of the hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine also occurs.
Dose-related gastrointestinal symptoms include pain, nausea, vomiting and diarrhoea.
Clofazimine tends to accumulate in the phagocytic monocytes of the small intestine. Prolonged treatment with doses higher than those recommended for the treatment of multibacillary disease has resulted in mucosal and submucosal oedema sever enough to produce symptoms of subacute small-bowel obstruction. Because of this rare but serious adverse effect it is recommended that the high dosages used in the treatment of erythema nodosum leprosum should be given only under medical supervision and for no longer than 3 months.
Drug interactions: Concurrent administration of clofazimine to leprosy patients receiving rifampicin with or without dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma level.

DAPSONE

Group: antileprosy agent
Tablet: 25 mg, 50 mg, 100 mg

General information

A sulfone that remains of prime importance in the treatment of leprosy. Dapsone is both bacteriostatic and weakly bactericidal against *M. leprae*, the minimum inhibitory concentration for fully sensitive organisms being approximately 0.003 micrograms/ml. However, resistant strains can develop *de novo* during prolonged treatment with dapsone alone, and their incidence is increasing in previously untreated patients. In some areas the prevalence of primary resistance is currently estimated to be as high as 40%.

After absorption from the gastrointestinal tract, dapsone is distributed widely in body tissues and it is subsequently retained selectively in skin, muscle, liver and kidneys. It is partially acetylated or conjugated in the liver and ultimately excreted in the urine as metabolites. A dose of 100 mg produces a peak serum concentration of approximately 2 micrograms/ml, which declines with a half-life of 1–2 days.

Clinical information

Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage:

Paucibacillary leprosy (in combination with rifampicin)

Adults: 100 mg daily for 6 months.

Children (10–14 years): 50 mg daily for 6 months

Children, less than 10 years: Adjust the dose. For example, dapsone, 25 mg daily for 6 months

Multibacillary leprosy (in combination with rifampicin and clofazimine)

Adults: 100 mg daily for 12 months

Children (10–14 years): 50 mg daily for 12 months

Children, less than 10 years: Adjust the dose. For example, dapsone, 25 mg daily for 12 months

Contraindications: Known hypersensitivity to sulfones; severe anaemia.

Precautions: Pre-existing severe anaemia should be treated before dapsone therapy is started. Dapsone can induce haemolysis of varying degree, particularly in patients with glucose-6-phosphate dehydrogenase deficiency, and dose-dependent methaemoglobinaemia may supervene during the second week treatment. The clinical response and blood count must therefore be closely monitored in susceptible patients during the first weeks of treatment. Dapsone therapy should not be discontinued if exacerbations occur.

Adverse effects: Dapsone is generally well tolerated at recommended dosages, but symptoms of gastrointestinal irritation occasionally occur. Other less common reactions include headache, nervousness and insomnia.

Blurred vision, paraesthesia, reversible neuropathy, drug fever, skin

rashes, and psychoses have also been reported. Hepatitis, Herxheimer reactions and agranulocytosis may rarely occur.
Drug interactions: Concurrent administration of clofazimine to leprosy patients receiving rifampicin with dapsone may decrease the rate of absorption of rifampicin and increase the time to peak plasma level.

MINOCYCLINE

Group: Antimicrobial (tetracycline) agent
Tablet, 50 mg, 100 mg

General information

Minocycline is a semisynthetic tetracycline. It induces bacteriostasis by inhibiting protein synthesis, and is selectively concentrated in susceptible organisms.
Absorption occurs mainly from the stomach and small intestine. Peak plasma concentrations occur within 1–4 hours and decay with a half-life of about 12–30 hours. It is metabolized to a considerable extent in the liver and is eliminated both in the urine and faeces. The drug persists in the body after its administration is stopped possibly due to retention in fatty tissues.

Clinical information

Uses: Single lesion paucibacillary leprosy in combination with rifampicin and ofloxacin. Treatment of multibacillary patients, who can not take rifampicin. Treatment of multibacillary patients, who refuse to take clofazimine.
Dosage:
Treatment of single lesion paucibacillary leprosy in combination with rifampicin and ofloxacin: Adults: single dose of 100 mg.

Treatment of multibacillary patients, who cannot take rifampicin: Treat for 24 months. The treatment regimen is:

Length of Treatment	Drug	Dose
6 months	clofazimine	50 mg daily
	ofloxacin	400 mg daily
	minocycline	100 mg daily
Followed by an additional		
18 months	clofazimine	50 mg daily
	plus either	
	ofloxacin	400 mg daily
	or	
	minocycline	100 mg daily

Treatment of patients with multibacillary leprosy, who refuse to take clofazimine.

Replace clofazimine in the normal 12 month multidrug therapy with minocycline, 100 mg daily.

An alternative 24 month multidrug therapy regimen (3 drugs), who refuse to take clofazimine is:

- rifampicin, 600 mg once a month for 24 months,
- ofloxacin, 400 mg once a month for 24 months, AND
- minocycline, 100 mg once a month for 24 months

Contraindications: Known hypersensitivity. Severe renal impairment. Pregnancy and early childhood. Do not give with iron salts or with antacids containing calcium, magnesium or aluminum.

Precautions: Monitor liver function prior to administration. In impaired liver function, minocycline may be excreted more slowly than expected. Tetracyclines may cause photosensitivity so patient should avoid exposure to sunlight. Troublesome oesophagitis may be averted if the patient is propped up while swallowing capsules, and washes them down immediately with a glass of water. Capsules and tablets should not be taken with milk or with magnesium or aluminium salts since these impair the absorption of minocycline.

Use in pregnancy

Minocycline is generally contraindicated in pregnancy and during early childhood. Because it is deposited in developing teeth and bones and impairs skeletal calcification, it can result in abnormal osteogenesis and permanent staining of teeth, and occasionally causes hypoplasia of dental enamel.

Adverse effects: Vestibular disturbances, causing dizziness and vertigo occur more commonly than with other tetracyclines. Gastrointestinal irritation is common as is depletion of the normal bowel flora, permitting overgrowth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with coagulase-positive staphylococci, and from pseudomembranous colitis due to Clostridium difficile. Phototoxic reactions occasionally result in porphyria-like skin changes and pigmentation of the nails.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis have been reported, as have angioedema, anaphlyaxis and pseudotumour cerebri.

A single dose of minocycline is used in children for treatment of single lesion paucibacillary leprosy. Field trials have shown that a single dose of minocycline is well tolerated in children and field trials have not detected any significant adverse effects due to a single dose of minocycline in children.

Drug Interactions: The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking tetracyclines. Antacids, calcium salts, and ulcer healing drugs (sucralfate) reduce absorption of minocycline. Antiepileptics increase metabolism of minocycline, leading to reduced plasma concentration of minocycline.

OFLOXACIN

Group: antimicrobial (quinolone) agent
Tablets, 200 mg, 400 mg

General information

Ofloxacin is a synthetic fluoroquinolone which acts as a specific inhibitor of bacterial DNA gyrase. It has been found to be efficacious in the treatment of *Mycobacterium leprae*. Reports of chromosome resistance have been reported but as yet are of relatively little clinical significance.

It is rapidly absorbed from the gastrointestinal tract. Peak plasma levels occur 0.5-1.5 hours after dosing. It is widely distributed in body tissues and is concentrated in the bile. It has a plasma half-life of 4 hours and is excreted in the urine mainly as unchanged drug.

Clinical information

Uses: Single lesion paucibacillary leprosy in combination with rifampicin and minocycline. Treatment of patients with multibacillary leprosy, who cannot take rifampicin. Treatment of patients with multibacillary leprosy, who refuse to take clofazimine.

Dosage:

Treatment of patients with single lesion paucibacillary leprosy in combination with rifampicin and minocycline

Adults: single dose of 400 mg. Children: single dose of 200 mg

Treatment of patients with multibacillary leprosy, who cannot take rifampicin. Treat for 24 months. The treatment regimen is:

Length of Treatment	Drug	Dose
6 months	clofazimine	50 mg daily
	ofloxacin	400 mg daily
	minocycline	100 mg daily

Followed by an additional		
18 months	clofazimine	50 mg daily
	plus either	
	ofloxacin	400 mg daily
	or	
	minocycline	100 mg daily

Treatment of patients with multibacillary leprosy, who refuse to take clofazimine.

Replace clofazimine in the normal 12 month multidrug therapy for patients with multibacillary leprosy with ofloxacin, 400 mg daily.

An alternative 24 month multidrug therapy regimen (3 drugs) for adult patients with multibacillary leprosy, who refuse to take clofazimine is:

- rifampicin, 600 mg once a month for 24 months,
- ofloxacin, 400 mg once a month for 24 months, AND
- minocycline, 100 mg once a month for 24 months

Contraindications: Hypersensitivity to any quinolone.

Precautions: Patients with hepatic or renal impairment may require reduced dosage.

Ofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated. Ensure adequate fluid intake since crystalluria may occur.

Quinolones, such as ofloxacin have been shown to cause arthropathy (degenerative changes in weight bearing joints) in young *animals*, so use with caution in children and adolescents, pregnant women or breast-feeding mothers. Field trials with a single dose of ofloxacin in children for the treatment of single lesion paucibacillary leprosy have not shown adverse effects.

Patient should avoid exposure to sunlight. Wait at least 4 hours before giving any product containing aluminium, iron or magnesium salts. Give with a full glass of water.

Adverse effects: Ofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, rash, dizziness and pruritus.

Drug Interactions: Taking non-steroidal anti-inflammatory drugs with ofloxacin may induce convulsions. Antacids reduce absorption of ofloxacin. Anticoagulant effect of coumarin and warfarin increased by ofloxacin. Antidiabetics: effect of sulphonylureas enhanced. Oral iron reduces absorption of ofloxacin. Sucralfate reduces absorption of ofloxacin.

PREDNISOLONE

Group: corticosteroid
Tablet, 5 mg

General information

Prednisolone is a synthetic glucocorticoid with weak mineralocorticoid properties. Its therapeutic effects result from inhibition of macrophage accumulation, suppression of capillary wall permeability, and reduction of fibroblast proliferation and collagen deposition. It is readily absorbed from the gastrointestinal tract, is extensively protein-bound and has a plasma half-life of about 8 hours.

Clinical information

Uses: Treatment of neuritis in leprosy patients. Treatment of severe lepra reactions. Treatment of inflammation in the eye in leprosy patients.
Dosage: The usual course of oral prednisolone treatment begins with 40-60 mg daily up to a maximum of 1 mg/kg body weight. Oral prednisolone treatment is then gradually reduced each week or every second week and is stopped after 12 weeks of treatment.
The standard 12 week oral prednisolone treatment for an adult patient follows:

Dose once a day	Week of Treatment
40 mg	1, 2
30 mg	3, 4
20 mg	5, 6
15 mg	7, 8
10 mg	9, 10
5 mg	11, 12

Contraindications: Active bacterial, viral or fungal infections.
Precautions: Patients must remain under close medical supervision. Body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentrations should be monitored throughout treatment. Bone pain and particularly backache, may be indicative of osteoporosis. Use with great caution in patients with hypertension, diabetes mellitus, epilepsy, glaucoma, peptic ulcer, a history of mental disorder or psoriasis. Patients with a history of tuberculosis should receive prophylactic chemotherapy.
Patients taking prednisolone are more susceptible to infection and the severity of infection may be increased. Additionally, prednisolone therapy may mask the symptoms of infection until the infection is in an advanced stage.
Do not give live vaccines (for example, oral polio, chickenpox, measles, mumps, rubella, yellow fever) while the patient is taking corticosteroids. Unless the patient has had chickenpox or measles, that patient is at risk of severe cases of these diseases during prednisolone therapy so the patient must take special care to avoid exposure to these infections.
Use in pregnancy: Systemic corticosteroid preparations should not be administered during pregnancy unless the need of the mother outweighs any possible risk of harm to the fetus. Adrenal development may be impaired and an association with cleft palate and other fetal abnormalities has been described. Dosage should be kept as low as possible.
Adverse effects: Adverse effects are dependent upon dosage and duration of therapy.
Doses in excess of 20 mg daily are immunosuppressive. Infections contracted during therapy can be fatal in the absence of effective treatment.
Long-term treatment at dosages in excess of normal physiological requirements (approximately 10 mg daily) is liable to result in:
stunting of growth in children, which may be averted by giving corticotrophin and selecting alternate-day dosage schedules;
features of hypoercorticalism, including moon face, acne, bruising,

abdominal striae, trunkal obesity, muscle wasting, hypertension and amenorrhoea and hirsutism in females;
spinal osteoporosis and vertebral collapse, which may be retarded by giving calcium supplements and small doses of vitamin D;
aseptic osteonecrosis, particularly of the femoral head;
subcapsular cataracts and glaucoma;
development or aggravation of peptic ulcers;
diabetes mellitus;
depression and psychosis, with risk of suicide;
raised intracranial pressure and convulsions, particularly in children;
increased coagulability of blood;
delayed tissue healing;
myopathy, characterized by weakness of the proximal musculature of arms and legs.
Psoriasis may be seriously exacerbated on sudden withdrawal of systemic corticosteroid therapy.
Interactions: Hepatic enzyme inducers including phenobarbital, phenytoin and rifampicin may accelerate the metabolism of prednisolone. The response to oral anticoagulants may be altered. Inhibition is characteristic, but isolated cases of potentiation have been reported.
Concomitant administration of acetylsalicylic acid or nonsteroidal anti-inflammatory drugs may increase the incidence of gastrointestinal ulceration.
Concomitant administration of diuretics that inhibit the reabsorption of potassium increases the risk of hypokalaemia.

RIFAMPICIN

Group: antimycobacterial agent
Capsule or tablet 150 mg, 300 mg

General information

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens.

Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in 2–4 hours, which subsequently decays with a half-life of 2–3 hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.
Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

Clinical information
Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs. Treatment of patients with multibacillary leprosy, who refuse to take clofazimine.
Dosage:
Paucibacillary leprosy (in combination with dapsone)
Adults: 600 mg, supervised, once a month for 6 months.
Children (10-14 years): 450 mg, supervised, once a month for 6 months.
Children, less than 10 years: Adjust the dose. For example, rifampicin, 300 mg, supervised, once a month for 6 months.
Multibacillary leprosy (in combination with dapsone and clofazimine)
Adults: 600 mg, supervised, once a month for 12 months.
Children (10-14 years): 450 mg, supervised, once a month for 12 months.
Children, less than 10 years: Adjust the dose. For example, rifampicin, 300 mg, supervised, once a month for 12 months.
Treatment of patients with multibacillary leprosy, who refuse to take clofazimine.
An alternative 24 month multidrug therapy regimen (3 drugs) for adult patients, who refuse to take clofazimine is:

- rifampicin, 600 mg once a month for 24 months,
- ofloxacin, 400 mg once a month for 24 months, AND
- minocycline, 100 mg once a month for 24 months

Contraindications: Known hypersensitivity to rifamycins. Hepatic dysfunction.

Precautions: Serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation, it should be immediately and definitively withdrawn. Careful monitoring of liver function is required in the elderly and in patients who are alcohol-dependent or who have hepatic disease.

Patients should be warned that treatment may produce reddish discolouration of urine, tears, saliva and sputum and that contact lenses may be irreversibly stained.

Adverse effects: Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more to occur with intermittent than with daily administration. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported. These reactions subside when daily dosage is substituted.

Moderate rises in serum concentrations of bilirubin and transaminases which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur, which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

Drug Interactions: Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, quinidine, ciclosporin and digitalis glycosides. Patients should consequently be advised to use a nonsteroidal form of birth control throughout the treatment and for at least 1 month subsequently.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B_{12} disturbed.