SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Minocycline Eurogenerics 100 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 115.85 mg minocycline hydrochloride dihydrate equivalent to 100 mg minocycline base.

Excipient with known effect:
One tablet contains 20 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Minocycline Eurogenerics 100 mg film-coated tablets are light yellow, oblong-formed, biconvex tablets with a smooth, mat surface (approximately 11.25 mm by 5.25 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Minocycline Eurogenerics 100 mg is used for treatment of
- uncomplicated non-gonococcal urethritis
- acute tracheobronchitis caused by Mycoplasma pneumonia
- trachoma (ocular infection caused by *Chlamydia trachomatis*)
- syphilis, actinomycosis or anthrax in patients allergic to penicillin.

See section 5.1 concerning micro-organisms that are susceptible to minocycline.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Usual dosages for most infections:

Adults: a dose of 200 mg on the first day, followed by a daily dose of 100 mg. For severe infections the dosage can be increased to 200 mg initially, followed by 100 mg every 12 hours.

Paediatric population
For children between 9 to 12 years old the usual initial dose is 4 mg/kg/day, followed by a dose of 2 mg/kg every 24 hours. Minocycline should not be prescribed to children under 8 years old.

Elderly: Clinical studies on minocycline hydrochloride contain an insufficient number of patients of 65 and older to assess whether this age group's reactions to treatment differs from that of younger patients. Caution is required when administering minocycline to elderly patients. Treatment should be initiated at the lowest possible dosage (one tablet every other day) in view of frequency of reduced hepatic, renal or heart function in these patients and/or the presence of other pathologies.

Dosage recommendations for particular infections:

Non-gonococcal urethritis
Tetracyclines have the advantage of being simultaneously effective against the pathogens of non-gonococcal urethritis resulting in reduced occurrence of post-gonococcal urethritis. The dosage for these acute non-gonococcal-infections for minocycline is 200 mg daily for seven days.

General remarks
Therapy should be continued for 1 to 3 days after the characteristic symptoms or fever have disappeared. Prolongation of therapy may be considered on the basis of clinical response to the treatment and susceptibility data.

Patients with hepatic and renal dysfunction:
Caution is required when prescribing minocycline to patients with hepatic dysfunction. (see section 4.4). Minocycline should not be prescribed to patients with severe hepatic dysfunction (see section 4.3).

In patients with renal dysfunction the total dosage should be reduced or the recommended individual dosage should be reduced and/or the intervals between dosages should be prolonged. The total dose in 24 hours should not exceed 200 mg.

Method of administration

Tablets should be swallowed with plenty of water to avoid oesophageal irritation. Patients should not lie down immediately after ingestion. Tablets may be taken during meals if ingestion causes stomach complaints. Absorption of minocycline is virtually not affected by simultaneous consumption of milk (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substance, to tetracyclines or to any of the excipients listed in section 6.1.
- Severe liver impairment.
- Pregnancy and lactation (see section 4.6).
- Severe renal insufficiency.

As for all tetracyclines, minocycline should not be administered to children under 8 years old (for children aged between 8 and 12 years see section 4.4).

4.4 Special warnings and precautions for use

Cross-hypersensitivity and cross-resistance between tetracyclines exists. When administering tetracyclines to women of child bearing potential pregnancy must be ruled out (see section 4.6). The anti-anabolic action of tetracyclines may cause an increase in blood urea (nitrogen) content. Although this does not necessarily pose a problem in persons with normal renal function, higher serum concentrations of minocycline may lead to azotaemia, hyperphosphataemia and acidosis in patients with significantly impaired function. With renal disorders even normal dosages may lead to excessive systemic

accumulations of the medicine and possibly to hepatic poisoning. Under such circumstances a total dosage lower than normal is indicated and if treatment is continued it may be advisable to determine the serum concentrations of the medicine.

Photosensitivity manifesting itself by abnormally severe sunburn reactions has been observed in patients treated with tetracyclines. Patients who are being exposed to direct sunlight or ultraviolet light should be advised that the above reactions may occur during treatment with tetracyclines.

Treatment should be discontinued on the first symptom of skin erythema. This reaction is rarely observed in using minocycline.

As with other antibiotic preparations, the use of this medicine may lead to excessive multiplication of the non-sensitive organisms, including fungi. The most significant super infections associated with the application of tetracyclines include intestinal super infections. If super infections start to develop, the antibiotics treatment should be discontinued and appropriate treatment should be initiated. When severe diarrhoea accompanied by fever occurs during treatment, pseudo membranous colitis or staphylococcal enteritis should be seriously considered as diagnosis. Discontinuance of the therapy may then be necessary; depending on the diagnosis either vancomycin or cloxacillin is administered orally and rehydration is carried out. Drugs inhibiting peristalsis are contraindicated.

Pseudo-tumour cerebri (benign intracranial hypertension) in adults is associated with the use of tetracyclines. The usual clinical syndromes are headache and blurred vision. Bulging fontanels are associated with the use of tetracyclines in young children. Although both of these disorders and the related symptoms disappear after discontinuing treatment with tetracyclines, after-effects may be permanent.

Symptoms of a vestibular nature have been observed during treatment with minocycline. These symptoms occur more frequently in women than in men and are reversible. When dizziness occurs, it may be desirable to adjust the dosage. Caution is required particularly in patients suffering from Meniere's syndrome. When vestibular symptoms and other side effects occur, such as visual disturbances, hallucinations and scotoma, treatment with minocycline should be terminated.

Tetracyclines can be hepatotoxic, especially when applied in high dosages and/or concomitantly with other hepatotoxic medicines or when hepatic or renal insufficiencies are pre-existent.

Isolated cases of systemic lupus erythematosus (SLE) and also exacerbation of pre-existing SLE have been reported.

In all of these cases administration of tetracyclines should be carried out under medical supervision (see also section 4.3). Increased excretion of ascorbic acid and folic acid has been observed during treatment with tetracyclines. This is generally of little clinical significance.

Prolonged tetracycline therapy may be accompanied by vitamin B deficiency as a result of the destruction of vitamin B producing bacteria.

Cases of abnormal thyroid function, such as thyroiditis, thyroid nodule, goitre and thyroid cancer, have been reported in patients taking minocycline during the post-marketing period (see section 4.8).
When minocycline therapy is given over prolonged periods, monitoring for signs of thyroid cancer should be considered.

Paediatric population
Children between 8 and 12 years of age should only be considered for treatment with minocycline when all other options are ineffective or contra-indicated.

Minocycline Eurogenerics contains lactose (a dose equivalent to 100 mg minocycline is responsible for 20 mg lactose monohydrate). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

If the treatment continues more than 6 months, some signs and symptoms of systemic lupus erythematosus and hepatitis may appear so this should be taken in consideration. If any of these symptoms appear the treatment should be immediately suspended.

Laboratory tests
In venereal diseases where also syphilis is suspected, a dark field test should be performed before commencing treatment. Also, blood serologic tests should be iterated monthly for at least 4 months. When used for prolonged periods, periodic laboratory tests of the organic system, amongst which haematopoietic, renal and hepatic examinations, should be carried out.

4.5 Interaction with other medicinal products and other forms of interaction

Tetracyclines form biologically inactive chelates with metal ions such as present in antacids and iron salts. Concomitant treatment with antacids or preparations containing antacids (e.g. didanosine) and iron preparations should be avoided. The interaction causes a reduction of the bio-availability of tetracyclines; on the other hand, absorption of iron ions is disturbed by tetracyclines.

Activated charcoal and ion exchangers have a negative effect on the absorption when administered concomitantly.

As tetracyclines may cause prolonged prothrombin times, they enhance the action of anticoagulants when administered concomitantly. Adjustments of the dosage of anticoagulants may become necessary.

Tetracyclines may antagonize the action of beta-lactam antibiotics. Concomitant administration of these antibiotics is advised against.

The combination of tetracycline therapies with methoxyflurane anaesthetics may cause renal damage.

Carbamazepine may cause decreased or subtherapeutic minocycline levels in concurrent use due to its hepatic microsomal enzyme induction.

When administered simultaneously, H2-antihistamins may reduce the bioavailability of minocycline.

Administration of isotretinoin should be avoided before, during and after treatment with minocycline hydrochloride. The combination of these two substances may increase the risk of intracranial hypertension. Each separate substance has been associated with cerebral pseudo-tumor.

Interactions with laboratory tests
Tetracyclines may interfere with glucose reactions in urine and catecholamines in urine.

4.6 Fertility, pregnancy and lactation

Pregnancy
Minocycline is contra-indicated. Observations in humans have proved that tetracyclines are damaging for the foetus, since they slow down osteogenesis, causing bones to become brittle and since they have a negative influence on the dental development (irreversible discoloration, hypoplasia of the dental enamel). On this ground and because of the risk of hepatic damage in the mother, use of minocycline during pregnancy is advised against (see section 4.3). When using tetracyclines in women of child-bearing potential pregnancy should be ruled out.

Breastfeeding
Tetracyclines are excreted in breast milk. Because of the adverse effects on the development of bones and teeth administration of minocycline during lactation is advised against (see section 4.3). If discontinuation of the therapy is undesirable lactation should be discontinued.

4.7 Effects on the ability to drive and use machines

Since symptoms of vestibular nature and visual disturbances can occur, minocycline should be avoided while driving or using machines.

4.8 Undesirable effects

The adverse drug reactions derived from clinical studies and post-marketing surveillance with minocycline, sorted by MedDRA System Organ Class are listed below.
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Discolouration of several tissues has been observed under minocycline therapy and was generally reversible upon termination of therapy.

The following side effects have been reported in patients treated with tetracyclines:

Infections and infestations:
Not known: Overgrowth of non-susceptible organisms, including fungi (see section 4.4)

Blood and lymphatic system disorders:
Uncommon: Thrombocytopenia, neutropenia and eosinophilia have been reported.
Rare: Haemolytic anaemia;
Prothrombin activity may be depressed;
Not known: agranulocytose.

Immune system disorders:
Uncommon: Urticaria, angioneurotic oedema
Rare: Polyarthralgia, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, pulmonary infiltrates with eosinophils have been reported. Also transient lupus-like syndrome (see section 4.4), serum sickness reaction and vasculitis have been reported in relation to minocycline hydrochloride therapy.
Not known: Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

Endocrine disorders:
Very rare: Brown-black microscopic discolouration of the thyroid glands has been reported in long term use of tetracyclines. Abnormal thyroid glandular functions, including thyroiditis, thyroid nodule, goiter and thyroid cancer, have been reported (see section 4.4).

Metabolism and nutrition disorders
Not known: Decreased level of vitamin B, ascorbic acid and folic acid (see section 4.4)

Psychiatric disorders:

Not known: Hallucinations

Nervous system disorders:
Rare: Bulging fontanels in children and benign intracranial hypertension (pseudo-tumour cerebri) in adults have been reported (see section 4.4). This may be accompanied by headache. These symptoms are reversible; the symptoms (headache and visual disturbances) usually disappear within a few days or weeks on discontinuation of the therapy, although the risk of permanent damage cannot be ruled out. There are also reports of: paraesthesia, convulsions and sedation.

Eye disorders:
Not known: Visual disturbances, scotoma and double vision. Pigmentation of cornea, sclera and retina has been observed.

Ear and labyrinth disorders
Not known: Vestibular disturbances, vertigo

Vascular disorders
Not known: Polyarteritis nodosa

Gastrointestinal disorders:
Rare: Anorexia, nausea, vomiting, diarrhoea; Oesophagitis and oesophageal ulceration were reported in patients treated with antibiotics belonging to the group of tetracyclines available in capsules or tablet forms. The greater part of these patients took the medicine just before retiring to bed (see section 4.2).
Discolouration of the teeth in children under 8 years of age, as well as in adults, although rarely, has been reported (see section 4.3).
Inflammatory lesions with excessive Candida-growth in the anogenital area, pruritus ani, black tongue, stomatitis and increase in hepatic enzymes.
Very rare: Glossitis, epigastric pain, dyspepsia, dysphagia, enterocolitis including staphylococcal enteritis, pancreatitis, pseudo membranous colitis (see section 4.4)

Hepatobiliary disorders:
Rare: As with other tetracyclines, some functional hepatic values are increased. Hepatitis and hepatic disturbances were rarely reported.
Very rare: When used for a longer period of time hepatic damage, occasionally accompanied by pancreatitis, or hepatic or renal dysfunction and also acute hepatic failure was reported.

Skin and subcutaneous tissue disorders:
Rare: Alopecia, pruritus, maculopapular and erythematous rashes, exfoliative dermatitis (not very frequent). Erythema multiforme has been reported and, rarely (see section 4.4), Stevens Johnson syndrome. Photodermatitis has been described above (see section 4.4). Pigmentation of skin and mucous membrane has been reported with an increasing risk at higher cumulative dosage. For minocycline it is more often reported than for other tetracyclines. Pigmentation is generally reversible on cessation of therapy. Nail discolouration has been observed after long term use.
Not known: erythema nodosum

Musculoskeletal and connective tissue disorders:
Rare: Asymptomatic discolouration of bones has been observed.
Not known: The development of bones in children is adversely affected. Bones may become more brittle.

Renal and urinary disorders:
Rare: Report has been made of a raised blood urea (nitrogen) content, related to the dose and aggravation of azotaemia, hyperphosphataemia and acidosis in patients suffering from renal dysfunction (see section 4.4).

Very rare: reversible acute renal dysfunction was reported.

General disorders and administration site conditions:
Uncommon: Pyrexia

Investigations:
Information about laboratory tests see section 4.4

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms are mainly gastrointestinal and central nervous system symptoms: hepatic damage with symptoms such as vomiting, bouts of fever, icterus, haematomas, melaena, azotemia, raised transamination values, prolonged prothrombine time (see section 4.8 and 4.4).

There is no specific antidote. After ingestion let the patient drink water, induce vomiting, gastric lavage (at large quantities), and purge. Administer antacids to reduce absorption. Furthermore, any symptoms of overdosing should be treated and supportive measures should be taken. Available data indicate that peritoneal dialysis or haemodialysis are of little value.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: General anti-infectives for systemic use, antibacterials for systemic use, tetracyclines, ATC code: J01AA08

Minocycline has a bacteriostatic effect based upon inhibition of the protein synthesis. Minocycline and doxycycline have a greater *in vitro* activity on Gram-positive bacteria than tetracycline, as a result of which some tetracycline resistant strains *in vitro* are still sensitive to minocycline and doxycycline. Minocycline is also effective against many staphylococcal strains resistant to penicillin G. *In vitro* susceptibility has been shown for Listeria monocytogenes. No clinical trials on *in vivo* efficacy against Listeria monocytogenes infections have been reported. Bacteria which are resistant to minocycline *in vitro* are usually also resistant to the other tetracyclines.

The MIC breakpoints for susceptibility of minocycline are based on the Muller-Hinton-Agar dilution method:
S < 1 mg/l
I = 1 to 4 mg/l
R > 4 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species. Therefore, the local resistance situation should always be reviewed, especially when treating severe infections. The information provided here gives only approximate guidance on the probability of specific species being susceptible to minocycline.

Categorisation of microorganisms is based on susceptibility breakpoints as mentioned above:

COMMONLY SUSCEPTIBLE SPECIES
Aerobic gram-positive microorganisms: n.a.
Aerobic gram negative microorganisms: n.a.
Anaerobic microorganisms: *Propionibacterium acnes (*)*
Others: *Borrelia burgdorferi* *Chlamydiae (*)* *Coxiella burnetti* *Leptospira* *Mycoplasma (pneumoniae) (*)* *Rickettsiae* *Treponema pallidum* *Ureaplasma (urealyticum)*

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic gram positive microorganisms: *Bacillus anthracis* *Listeria monocytogenes* *Staphylococcus aureus* *Streptococcus epidermidis* *Streptocuccus pneumonia* *Streptococcus pyogenes* *Streptococcus viridans*
Aerobic gram-negative microorganisms: *Brucella* *Escherichia coli* *Haemophilus influenza* *Klebsiella pneumonia* *Neisseria gonorrhoeae* *Pasteurella* *Salmonella* *Shigella* *Vibrio cholerae*
Anaerobic microorganisms: *Bacteroides* and other pure anaerobes

INHERENTLY RESISTANT ORGANISMS
Pseudomonas *Proteus* *Serratia* *Providencia* *Enterococcus faecalis*

(*) Species in which it is considered that activity has been satisfactorily demonstrated in clinical studies.

5.2 Pharmacokinetic properties

Absorption
After oral administration minocycline is virtually completely absorbed. 2-3 hours after a single oral administration of 200 mg, 150 mg, 100 mg minocycline maximum serum concentrations are reached of approx. 3.2 µg/ml, 2.2 µg/ml and 1.2 µg/ml respectively. After 24 hours these serum levels decrease to a therapeutic minimum of approx. 0.7 µg/ml. The absorption of minocycline is practically not affected by concomitant consumption of milk. Absorption of minocycline is delayed when taken simultaneously with food (approx. 1 hour); the rate of absorption is hardly affected. Tetracyclines are subject to the enterohepatic cycle.

Distribution
Minocycline distributes into body tissues resulting in higher concentrations in the brain and the liquor cerebrospinalis than with other tetracycline homologues. Minocycline serum and tissue concentrations turn out to be approximately two to four times higher in comparison with tetracycline. Minocycline accumulates in dentine and bone. Plasma protein binding of minocycline is approximately 70-75%. Minocycline crosses the placenta and is excreted in breast milk. Minocycline reaches high concentrations in tears and saliva.

Biotransformation
Minocycline is partly metabolized in the organism into non-active compounds, probably by the liver. The plasma half-life of minocycline is approx. 12-16 hours.

Elimination
The excretion of minocycline chlorohydrate is the same after intravenous or oral administration. In urine 5-6% of the administered dosage is excreted unchanged after 24 hours and approx. 9% after 48 hours. After administration of radioactively labelled minocycline 86% of the radioactivity can be retraced, mainly in the faeces and urine (of which 31% as unchanged minocycline at a single dosage).

5.3 Preclinical safety data

Animal tests show that minocycline at high dosages does not cause acute toxicity, with chronic administration of very high dosages, however, symptoms have been observed, such as discolouration of the bones and teeth.

Animal tests indicate that tetracyclines cross the placenta. Tetracyclines have been found in foetal tissues. Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

There is little or no information about mutagenic or carcinogenic potential of minocycline.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K25
Lactose monohydrate
Microcrystalline cellulose (E460)
Croscarmellose sodium
Colloidal silicon dioxide (E551)
Magnesium stearate (E470b)
Hypromellose 2910
Macrogol 6000 (E1521)

Yellow iron oxide (E172)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister packs with 10, 20, 30, 40, 42, 50, 80, 84, 90, 98, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eurogenerics NV
Heizel Esplanade b22
1020 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

RVG 110441

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 1 november 2012
Datum van laatste verlenging: 4 oktober 2017

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.8: 12 februari 2023