SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metrolag®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains: Metronidazole 250mg or 500 mg.
100 ml solution for IV infusion contain: Metronidazole 500 mg.

Excipient(s) with known effect
Metrolag 250 mg contains 50 mg Lactose in each tablet
Metrolag 500 mg contains 47.5 mg Lactose in each tablet

Metrolag 500 mg contains 0.15 mg of sodium
Metrolag i.v. contains 334.4 mg/100 ml of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Solution for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metrolag is indicated for the treatment of infections if the presence of anaerobic bacteria is proven or suspected while taking under consideration the spectrum of activity of metronidazole.

Metrolag, in the form of tablets, can be used in cases of amebiasis (intestinal or hepatic), Trichomonas infections of the urogenital tract, Gardnerella vaginalis infections and in the case of lambliasis.

Metrolag solution for intravenous infusion is used in sepsis, bacteraemia, brain abscess, necrotizing pneumonia, osteomyelitis, puerperal fever, abscess of the pelvis, parametritis, peritonitis and infections post-operative wounds if anaerobic germs have been isolated.

Metrolag i.v. also helps to prevent and treat post-operative infections due to anaerobic bacteria, particularly if the germ is a Bacteroides.

As metronidazole is not active against aerobic bacteria, in infections caused by these or mixed infections (aerobic and anaerobic) adequate complementary chemotherapy should be instituted.

Please consult the official recommendations for the appropriate use of antibiotics, in particular the recommendations aimed at reducing the increase in resistance against antibiotics.

4.2 Posology and Method of administration

Tablets can be used in children from 6 years old under the following conditions:

- able to swallow a tablet,
- body weight compatible with the recommended unit dose (see below).

Metrolag 250 mg and 500 mg tablets have a score line which is decorative only and should not be broken at the score line.

Tablets

Gardnerella vaginalis – vaginitis (non-specific)

Two treatment regimens are applicable:

Either 1.0 to 1.5 g of metronidazole per day (= 2 to 3 tablets of 500 mg) for 5 to 7 days

Or 2.0 g of metronidazole (= 4 tablets of 500 mg) taken once on the first day of treatment, followed by a second identical dose (2.0 g = 4 tablets of 500 mg) on the third day of treatment.

The same treatment is recommended for the partner.

Trichomonas infections, Trichomonas urethritis and vaginitis

Two treatment regimens are applicable:

Either one time therapy (single dose): single dose and preferably in the evening of 2 g of metronidazole (= 4 tablets of 500 mg)

Or standard therapy (10 days): for 10 days, morning and evening, each time with a 250 mg tablet of metronidazole.

To prevent re-infection, the partner should always be treated with the same oral dose.

Amebiasis

Adults: 1 tablet of 500 mg metronidazole 3 to 4 times a day.

Children: 40 mg metronidazole/kg body weight/day divided into 3 to 4 doses. The 250 mg tablets are suitable for children from 19 kg body weight.

Duration of treatment: in acute intestinal or hepatic amoebiasis, 7-10 days.

Lambliasis

Cure of five consecutive days:

Adults: 1 tablet of 250 mg metronidazole 3 times a day.

Children: 15 mg metronidazole/kg body weight/day divided into 3 intakes. The 250 mg tablets are suitable for children from 50 kg body weight.

If necessary, the cure can be repeated after 8 days of interruption.

Anaerobic germ infections

Tablets: 1.5 g of metronidazole/day divided into 3 partial doses (= 3×1 film-coated tablet of 500 mg/day), possibly combined with an active substance against aerobic germs. The minimum duration of therapy is usually 10 days.

For treatment durations longer than 10 days, see 'Warnings and precautions'.

Solution for intravenous infusion

Intravenous administration of metronidazole should be limited to patients for whom oral therapy is not possible. Intravenous infusion therapy should be replaced by oral therapy as soon as possible. Metrolag i.v. is a ready-to-use solution for infusion. Metrolag can be

administered alone or at the same time (however without mixing) with other antibacterial chemotherapies if these are indicated (see "Warnings and Precautions"). Metrolag should be administered with an intravenous infusion rate of 5 ml/minute.

The drug treatment is generally done over a period of 5 to 7 days. The duration of treatment should not exceed 10 days. Only when absolutely necessary and accordingly, the treatment may be extended.

Only perfectly clear solutions can be used.

Treatment of anaerobic germ infections

Adults and children over 12 years of age: initial dose of 15 mg metronidazole (= 3 ml Metrolag i.v.) per kg of body weight followed by a maintenance dose of 7.5 mg metronidazole (= 1.5 ml of Metrolag i.v.) per kg of body weight every 6 hours for 3 days, then every 12 hours from the 4th day of treatment.

Maximum daily dose: 4 g of metronidazole.

Duration of the treatment; usually 7–10 days, severe anaerobic infections may require 2–3 weeks therapy.

Treatment of anaerobic germ infection in children under 12 years old

7.5 mg metronidazole (= 1.5 ml Metrolag i.v.) per kg of body weight every 8 hours for 3 days, then every 12 hours from the 4th day of treatment.

Prophylaxis of postoperative anaerobic infections

Adults and children over 12 years: 15 mg metronidazole intravenously (= 3 ml Metrolag i.v.) per kg of body weight over 30–60 minutes. The infusion should be completed 1 hour before the start of surgery. If necessary, an additional dose of 7.5 mg metronidazole (= 1.5 ml Metrolag i.v.) per kg of body weight can be given 6 (–8) and 12 (–16) hours after the operation. bodily.

Children under 12 years of age: As for adults, the dose is 7.5 mg metronidazole (= 1.5 ml Metrolag i.v.) per kg of body weight.

Special dosages

Renal failure

Metrolag can be used at normal doses in renal failure. However, the shortened half-life of metronidazole in haemodialysis patients should be considered. An additional dose may thus be necessary after haemodialysis. There is accumulation of metabolites of metronidazole in patients whose creatinine clearance is less than 10 ml/min and who are not on haemodialysis. These metabolites are rapidly eliminated by haemodialysis. The peritoneal dialysis is not effective.

Hepatic impairment:

In severe hepatic impairment, the dose should be reduced and the plasma concentration of metronidazole should be monitored.

4.3 Contraindications

Hypersensitivity to imidazole derivatives.

4.4 Warnings and Precautions

As a rule, the duration of treatment with Metrolag or with other nitroimidazole drugs cannot exceed 10 days. The treatment can only be extended beyond this period of time in exceptional cases and in very specific indications. It should also be repeated as

infrequently as possible. It is imperative to limit the duration of the treatment because it cannot be ruled out that the latter causes lesions in the gametes in humans. In addition, an increase in certain tumours has been observed in experimental studies conducted on animals.

During therapy with high doses or in the event of abnormalities in the blood count, regular biological and clinical checks are indicated.

If compelling reasons dictate administration of Metrolag for longer than the recommended duration (duration of treatment of more than 10 days), the blood count, in particular the leukocyte count, should be checked at regular intervals. In addition, the patient should be monitored for the occurrence of adverse effects, such as peripheral and central neuropathies (eg paraesthesia, ataxia, vertigo, seizures).

Haematology: In patients whose history reveals blood dyscrasia, a white blood cell count should be done before and after treatment, especially if it is repeated.

Kidney failure and haemodialysis: see special posology in the "Dosage/Instructions" section.

Hepatic impairment: In severe hepatic impairment, the dose should be reduced, and the plasma concentration of metronidazole should be monitored. Metrolag should be used with caution in patients with hepatic encephalopathy.

Cockayne syndrome: Cases of severe hepatotoxicity/acute liver failure, including cases with fatal outcome, occurring rapidly after initiation of treatment, have been reported in patients with Cockayne syndrome during treatment containing metronidazole for systemic use. For this population, metronidazole should be used after careful benefit-risk assessment and only if no alternative treatment is available.

Liver function tests should be performed before initiation of treatment, during and after the end of treatment until liver function returns to normal or until target values are reached. If liver function tests show a significant elevation during treatment, treatment should be discontinued.

Patients with Cockayne syndrome should be instructed to report any signs of liver damage to their physician immediately and discontinue their treatment with metronidazole.

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP) have been reported with metronidazole (see section 'Undesirable effects'). If symptoms or signs of SJS, TEN or AGEP appear, Metrolag should be discontinued immediately and is contraindicated for further administration of metronidazole alone or in combination.

Nervous system: Serious active diseases of the central or peripheral nervous system may worsen during therapy with metronidazole, therefore metronidazole should be used with caution. If peripheral neuropathies, ataxias, dizziness or hallucinations occur, treatment should be discontinued.

Lithium therapy: Lithium retention accompanied by warning signs of possible renal failure has been observed in patients receiving metronidazole therapy concurrently with lithium therapy. Therefore, lithium therapy should be reduced or discontinued before starting treatment with Metrolag. Plasma lithium concentration, creatinine and plasma electrolyte values should be monitored in patients receiving lithium therapy.

Alcohol: due to the Antabuse effect of metronidazole (flush, vomiting, tachycardia), the patient should be informed to refrain from the consumption of alcoholic beverages and drugs containing alcohol during treatment with Metrolag and the day after.
Candidiasis: Pre-existing candidiasis may worsen during treatment with Metrolag.
Carcinogenesis, mutagenesis: Due to mutagenicity and carcinogenicity, particular care should be taken when exceeding the recommended therapeutic duration (see section "Preclinical data").
Suicidal behaviour and psychiatric disorders
Cases of suicidal ideation with or without depression have been reported during treatment with metronidazole. Patients are advised to stop their treatment and seek immediate medical attention if they experience psychiatric symptoms during treatment. Particular caution is required in patients with repeated or prolonged use of metronidazole and in patients with a history of alcoholism or parkinsonism due to a risk of psychosis. Simultaneous use of metronidazole and disulfiram can also predispose a patient to psychosis.
Metrolag tablets contain lactose. Patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.
Metrolag 500mg tablets contain less than 1mmol (23mg) sodium per tablet, i.e. that they are essentially "sodium free".
Metrolag solution for intravenous infusion contains up to 334.4 mg (15.2 mmol) sodium per 100 ml bag, which is equivalent to 16.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This is to be taken into consideration in the event of a controlled low-sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Metronidazole may increase the activity of oral anticoagulants (such as warfarin). If necessary, the thromboplastin time should be monitored, and the dosage of oral anticoagulant adjusted if necessary.
Administration of disulfiram (Antabuse) and metronidazole at the same time may result in psychotic reactions (see "Undesirable effects").
The administration of metronidazole at the same time as phenobarbital or phenytoin and other enzyme inducers has the consequence of reducing the serum half-life of metronidazole.
Enzyme inhibitors (e.g. cimetidine) increase the plasma half-life of metronidazole.
Plasma lithium concentrations may be increased by metronidazole. Regarding the interactions between Metrolag and treatments with lithium salts or Metrolag and the absorption of alcohol, please refer to the limitations of use.
Simultaneous administration of metronidazole and ciclosporin carries the risk of elevated serum ciclosporin levels. If the combination of these two drugs proves to be essential, the serum level of ciclosporin and serum creatinine should be monitored.
Metronidazole reduces the clearance of 5-fluorouracil and thus increases its toxicity.
In combination with busulfan, high toxicity has been reported. Therefore the concomitant intake of busulfan and metronidazole is not advised.

Drugs that prolong the QT interval: QT interval prolongation has been reported, particularly when metronidazole is used with drugs that may prolong the QT interval.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Since metronidazole readily crosses tissues, the placenta does not represent a barrier. The substance reaches high concentrations in breast milk (more than 50% of serum concentration).

The safety of metronidazole use during pregnancy has not been sufficiently demonstrated. Conflicting reports exist especially with regard to the onset of pregnancy. Some studies have found higher rates of malformations. The risk of possible late sequelae, including the carcinogenic risk, is not known to date. Use during the first trimester is contraindicated. During the second and third trimesters, metronidazole should only be used when there is a strict indication.

In the event of unrestricted use of nitroimidazoles by the mother, the unborn child or newborn is at risk of cancer or chromosomal damage. To date, there is no reliable opinion indicating an adverse effect on the embryo or fetus.

Breast-feeding

Breast-feeding is contraindicated during the use of Metrolag (until 24 hours after the last intake).

4.7 Effects on ability to drive and use machines

Since Metrolag can cause various nervous system and eye disorders (see "Undesirable effects"), the ability to drive and use machines may be reduced.

4.8 Undesirable effects

The Undesirable effects caused by Metrolag are generally dose-dependent.

The following frequencies were used: "very common" (≥1/10), "common" (≥1/100, <1/10), "uncommon" (≥1/1000, <1/100), "rare (≥1/10,000, <1/1000), "very rare" (<1/10,000), "not known" (frequency cannot be estimated from the available data).

Infections and infestations

Rare: genital superinfection (moniliasis).

Blood and lymphatic system disorders

Unknown frequency: haematological disturbances such as leukopenia, agranulocytosis, neutropenia, thrombocytopenia and bone marrow depression. If these side effects occur, treatment should be discontinued.

Immune system disorders

Frequency not known: hypersensitivity reactions such as angioedema and anaphylactic shock.

Psychiatric disorders

Frequency not known: psychotic disorders including confusion or hallucinations, depressed mood, suicidal ideation.

Nervous system disorders

Common: headache, dizziness.

Frequency not known: Peripheral neuropathies (eg sensory disturbances), depression, insomnia, weakness, ataxia, convulsions, aseptic meningitis.
Patients should be informed of the possible risk of serious adverse central nervous system effects. Patients should stop treatment and notify the doctor if such reactions occur.
Encephalopathy (eg confusion, vertigo, fever, headache, hallucinations, paralysis, sensitivity to light, stiff neck) and subacute cerebellar syndrome (eg vertigo, ataxia, dysarthria, weakness in gait, tremors, nystagmus), which may be reversible on discontinuation of treatment.
Eye disorders
Frequency not known: Transient visual disturbances such as diplopia, myopia, blurred vision, decreased visual acuity, change in color vision, optic neuropathy/neuritis.
Ear and labyrinth disorders:
Isolated cases: hearing loss/impairment (including neurosensory), ringing.
Heart disorders
Frequency not known: QT interval prolongation has been reported, particularly when metronidazole is used with drugs that can prolong the QT interval.
Gastrointestinal disorders
Common: nausea, vomiting, diarrhoea, taste disturbances, anorexia.
Frequency not known: epigastric disorders, inflammation of the oral mucosa, pseudomembranous colitis. At the onset of persistent diarrhoea, the treatment must be stopped immediately and an appropriate treatment (vancomycin) administered. In this case, the administration of products promoting faecal stasis is strictly prohibited.
Pancreatitis (reversible), tongue discoloration, pasty tongue (due to fungal overgrowth).
Hepatobiliary disorders
Frequency not known: increased liver enzymes (AST, ALT, alkaline phosphatase), and cholestatic or mixed hepatitis and hepatocellular damage sometimes associated with jaundice.
Cases of hepatic failure requiring liver transplantation have been reported in patients treated with metronidazole in combination with other antibiotics.
Skin and subcutaneous tissue disorders
Common: pruritus
Frequency not known: transient skin eruptions, flush, urticaria and pustular rash, fixed pigmented erythema, acute generalized exanthemic pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis.
Kidney and urinary disorders
Rare: dysuria, cystitis, incontinence of urine.
One of the metabolites of metronidazole has the effect of making the urine darker.

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.

4.9 Overdose

After single doses of up to 15 g of metronidazole for suicidal intentions, cases of nausea, vomiting, hyperreflexia, ataxia, tachycardia, dyspnoea and disorientation have been observed. No death cases were reported.

Treatment in case of overdose: There is no specific antidote for metronidazole. In the event of an acute overdose, symptomatic treatment should be undertaken (gastric lavage, activated charcoal, hemodialysis).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Antibacterials for systemic use

ATC code:
P01AB01, J01XD01

Mechanism of action

Metronidazole, a synthetic derivative of the nitroimidazole group. It is effective against most anaerobic bacteria as well as protozoa.

The antibacterial and antiparasitic activity of metronidazole is due to inhibition of nucleic acid synthesis of susceptible bacteria and protozoa.

Pharmacodynamics Microbiology:

The following bacteria and protozoa are susceptible to Metronidazole bactericidal activity:

Sensitive micro-organisms:

Bacteroides (also B. fragilis), Fusobacterium spp., Peptococcus, Peptostreptococcus, Veillonella spp. as well as Clostridium spp. and Eubacterium spp., Campilobacter fetus, Gardnerella vaginalis. The MIC of susceptible anaerobic bacteria is between 0.1 and 8 µg/ml.

Moderately sensitive micro-organisms:

Actinomycetes, Propionibacterium (MIC 8-16 µg/ml).

Non-susceptible microorganisms:

Aerobic and facultative anaerobic bacteria (MIC >16 µg/ml).

Susceptible parasites:

Entamoeba histolytica, Trichomonas vaginalis (MIC <3 µg/ml), Giardia intestinalis (MIC 0.8-32 µg/ml), Balantidium coli.

Resistances:

Within the group of nitro-imidazoles, cross-resistances are the rule. Resistant strains of Trichomonas vaginalis or Bacteroides fragilis (or other anaerobic bacteria) have rarely appeared after long-term therapy. For Switzerland, the breakpoints can be extrapolated to one of the data from EUCAST (European Committee on Antimicrobial Susceptibility Testing). The threshold values of MICs (minimum inhibitory concentrations) according to EUCAST, version 12.0, January 01, 2022 (www.eucast.org), are presented in the following table:

Microorganisms	Sensitive	Resistant
Gram-positive anaerobes (except Clostridioides difficile)	≤4 mg/L	>4 mg/L
Clostridioides difficile	≤2 mg/La	>2 mg/La
Helicobacter pylori	≤8 mg/L	>8 mg/L
Gram-negative anaerobes	≤4 mg/L	>4 mg/L
PK/PD thresholds (not species related)b	DI	DI

a Breakpoints are based on ECOFF (Epidemiological cutOFF) values and relate to oral treatment of C. difficile infections with metronidazole.

There are no conclusive clinical data regarding the relationship between MIC values and clinical response.

b DI indicates that the data are insufficient to show that the species in question is an adequate target for treatment with the drug. Clinical Efficacy

5.2 Pharmacokinetic Properties

Absorption

A dose of metronidazole administered orally is at least 80% absorbed by the gastrointestinal tract. After oral administration of a single dose of 250 mg, 500 mg or 2 g of metronidazole, peak plasma concentrations of 4.6–6.5 µg/ml, 11.5–13 µg/ml or 30 –45 µg/ml are respectively reached after 1–3 hours. If food is eaten at the same time as the drug, the resorption of the drug is somewhat slowed down, but not diminished.

After intravenous infusion of a dose of 500 mg of metronidazole over 20 minutes, the mean serum concentration is 18 µg/ml.

During intravenous infusion of a dose of 500 mg of metronidazole every 8 hours, the mean serum concentration of the substance is 14 µg/ml, the measured trough serum concentrations were always above the minimum inhibitory concentrations or the trough concentrations bactericides for sensitive germs.

Distribution

Plasma protein binding is low (less than 20%). Metronidazole diffuses rapidly and into virtually all tissues. Metronidazole is found mainly in the lungs, kidneys, liver, skin, bile, cerebrospinal fluid, saliva, semen and in vaginal secretions; it passes the placental barrier and into breast milk.

Metabolism

The liver metabolizes 30-60% of an orally or i.v. dose. The major metabolite also has some activity against bacteria and protozoa.

Elimination

Elimination is mainly via the kidneys (up to 80% in 48 hours), it is mainly the metabolites that are eliminated. The plasma half-life is 6-8 hours.

Kinetics for certain groups of patients

Renal failure: the plasma half-life is not modified. In hemodialysis patients, it is shortened and is only 2½ hours. Renal elimination decreases with increasing age.

Hepatic impairment: plasma half-life may be prolonged.

Newborns: Plasma half-lives are increased in neonates.

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5.3 Preclinical safety data

Genotoxicity

Metronidazole has shown a mutagenic effect in in vitro tests with bacteria. Conflicting results regarding the genotoxic effect have been reported in mammalian cells in studies performed in vitro and in vivo in rodents as well as in humans.

Carcinogenicity

Metronidazole has been shown to be carcinogenic in mice and rats. Similar studies in hamsters, however, showed negative results.

It is imperative to limit the duration of the treatment because it cannot be ruled out that the latter causes lesions in the gametes in humans. In addition, an increase in certain tumors has been observed in experimental studies on animals.

Reproductive toxicity

Animal experiments in rats with doses up to 200 mg/kg of body weight and in rabbits with doses up to 150 mg/kg of body weight per day have not shown any teratogenic effects or other embryotoxic effects. From 350 mg/kg, adverse effects were also recorded in the male reproductive system after repeated administration to rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metrolag 250 mg tablet:

Microcrystalline cellulose, Maize starch, Lactose monohydrate 50mg, Gelatine, Magnesium stearate.

Metrolag 500 mg tablet:

Microcrystalline cellulose, Maize starch, Lactose monohydrate 47.5mg, Gelatine, Magnesium stearate, Sodium starch glycolate corresp. Sodium 0.15mg

Metrolag Solution for intravenous infusion 500mg/100ml:

Sodium chloride corresp. Sodium 334.4mg/100ml; Water for injectation q.s. to the solution for 100 ml

6.2 Incompatibilities

Combined therapy

Metrolag i.v. should not be administered in combination with other medicinal products.

Influence on diagnostic methods

Metronidazole influences SGOT and SGPT determinations which are based on decreased UV absorption due to oxidation of NADH to NAD. This results in too low values for the SGOTs and SGPTs.

6.3 Shelf life

Metrolag tablets 250 mg: 60 months.
Metrolag tablets 500 mg: 60 months.
Metrolag infusion 500 mg / 100 ml bag: 24 months

6.4 Special precautions for storage

Keep out of reach of children. Store in its original packaging, closed, at room temperature (15–25°C) and protected from light.

6.5 Nature and contents of container

Metrolag tablets 250 mg: pack of 20's, 100's and 1000's tablets. The tablets are blistered in PVdC/PVC/Alu blisters in 10 tablets per blister. Blisters are packed in a pre-printed, white cardboard box. 10 or 100 blisters are packed in a neutral cardboard box.

Metrolag tablets 500 mg: packs of 8's, 24's and 120's tablets. The tablets are blistered in PVdC/PVC/Alu blisters in 8 tablets per blister. Blisters are packed in a pre-printed, white cardboard box.

Metrolag infusion 500 mg / 100 ml: The solution is contained in a pre-printed PVC bags with two tubing ports, vial stopper and injection point. 10 bags are packed in a neutral printed carton box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Instructions for the plastic bag

Observe aseptic conditions!

1. Do not remove the protective case until ready to use, pull down following the mark.
2. By pressing on the plastic pocket, ensure that it is intact. Damaged plastic bags must be destroyed.
3. Only clear solutions should be used.
4. Hang up the plastic pouch and remove the gray protective cap.
5. Close the flow control of the infusion device and slightly twist the tip to insert it into the opening of the plastic bag.

Follow the instructions included with the infusion device.

Notes on the plastic bag

Avoid the presence of air in the plastic bag.

The plastic pouches do not lend themselves to successive connections, which would risk causing an air embolism.

After opening the protective case, the plastic bag must be used immediately.

7 MARKETING AUTHORISATION HOLDER

Lagap SA
Via Morosini 3
6943 Vezia
Switzerland

8 MARKETING AUTHORISATION NUMBER(S)

Metrolag 250: LAG/SWZ/007, 05374/07502/REN/2020, 08579/08265/VAR/2023
Metrolag 500: 04804/6307/NMR/2018, 08578/08264/VAR/2023

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Metrolag 250: 12/06/2012, 03/11/2016,

29/09/2020, 07-04-2023

Metrolag 500: 13/12/2019, 07-04-2023

10 DATE OF REVISION OF THE TEXT

February 2022