Directions for Use
Read carefully!

# Metronidazole Intravenous Infusion 500 mg

## 1. NAME OF THE MEDICINAL PRODUCT

Metronidazole Intravenous Infusion 500 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 5 mg of metronidazole
100 ml of solution contain 500 mg of metronidazole

*Excipients with known effect:*
1 ml solution contains

| | |
|---|---|
| Sodium chloride | 7.4 mg |
| Disodium phosphate dodecahydrate | 1.5 mg |

*Electrolyte content (per 100 ml):*

| | |
|---|---|
| Sodium | 14 mmol |
| Chloride | 13 mmol |

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Solution for infusion;
A clear and slightly yellow solution

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment and prophylaxis of infections caused by metronidazole susceptible microorganisms (mainly anaerobic bacteria).
Metronidazole is indicated in adults and children for the following indications:

- infections of the central nervous system (e. g. brain abscess, meningitis)
- infections of lung and pleura (e. g. necrotising pneumonia, aspiration pneumonia, lung abscess)
- endocarditis
- infections in the gastrointestinal tract and the abdominal area (e.g. peritonitis, liver abscess, postoperative infections after colonic and rectal surgery, purulent diseases in the abdominal and pelvic cavities)
- gynaecologic infections (e. g. endometritis, after hysterectomy or caesarean section, childbed fever, septic abortion)
- infections in the ear-nose-throat region (e. g. PLAUT-VINCENT-angina)
- bone and joint infections (e. g. osteomyelitis)
- gas gangrene
- septicaemia with thrombophlebitis.

In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole Intravenous Infusion 500 mg.

A prophylactic use is always indicated prior to operations with a high risk of anaerobic infections (gynaecologic and intra-abdominal operations) Consideration should be given to official guidance on the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

The dosage is adjusted according to the patient's individual response to therapy, her/his age and body weight and according to nature and severity of the disease.

The following dosage guidelines should be followed:

*Adults and adolescents:*

Treatment of anaerobic infections
Usually a single dose of 1500 mg (300 ml) is given on the first day of treatment followed by 1000 mg (200 ml) given as single doses on the subsequent days.
Alternatively, 500 mg (100 ml) may be given every 8 hours.
The duration of therapy is dependent on the effect of the treatment. In most cases a treatment course of 7 days will be sufficient. If clinically indicated, treatment may be continued beyond this time. (See also section 4.4.)

Prophylaxis against post-operative infection caused by anaerobic bacteria:
500 mg, with administration completed approximately one hour before surgery. The dose is repeated after 8 and 16 hours.

*Paediatric population*

Treatment of anaerobic infections

- Children > 8 weeks to 12 years of age:
  The usual daily dose is 20 – 30 mg per kg BW per day as a single dose or divided into 7.5 mg per kg BW every 8 hours.

Duration of treatment is usually 7 days.

Prophylaxis against postoperative infections caused by anaerobic bacteria:

- Children < 12 years:
  7.5 mg/kg (1.5 ml/kg) i.v. 8 hourly.

*Patients with renal insufficiency*
No dose reduction is required, see section 5.2.

In patients undergoing haemodialysis the conventional dose of metronidazole should be re-administered immediately after haemodialysis on dialysis days to compensate the escape of metronidazole during the procedure.

*Patients with hepatic insufficiency*
As serum half-life is prolonged and plasma clearance is delayed in severe hepatic insufficiency, patients with severe liver disease will require lower doses (see section 5.2).

**Method of administration**

Intravenous use.
The contents of one bottle are to be infused slowly i.v., i.e. 100 ml max. over not less than 20 minutes, but normally over one hour.
Metronidazole Intravenous Infusion 500 mg can also be diluted before administration, adding the medicinal product to an i.v. vehicle solution such as 0.9 % sodium chloride or 5 % glucose infusion solution.
Concurrently prescribed antibiotics are to be administered separately.

### 4.3 Contraindications

Hypersensitivity to metronidazole or other nitroimidazole derivatives or to any of the excipients listed in section 6.1.

### 4.4 Special warnings and precautions for use

In patients with severe liver damage or impaired haematopoiesis (e. g. granulocytopenia), metronidazole should only be used if its expected benefits clearly outweigh potential hazards.

Due to the risk of aggravation, metronidazole should also be used in patients with active or chronic severe peripheral and central nervous system diseases only if its expected benefits clearly outweigh potential hazards.

Convulsive seizures, myoclonus and peripheral neuropathy, the latter mainly characterized by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurological signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

In the case of severe hypersensitivity reactions (e.g. anaphylactic shock), treatment with Metronidazole Intravenous Infusion 500 mg must be discontinued immediately and established emergency treatment must be initiated by qualified healthcare professionals.

Severe persistent diarrhoea occurring during treatment or during the subsequent weeks may be due to pseudomembranous colitis (in most cases caused by *clostridium difficile*), see section 4.8. This intestinal disease, precipitated by the antibiotic treatment, may be life-threatening and requires immediate appropriate treatment. Anti-peristaltic medicinal products must not be given.

The duration of therapy with metronidazole or drugs containing other nitroimidazoles should not exceed 10 days. Only in specific elective cases and if definitely needed, the treatment period may be extended, accompanied by appropriate clinical and laboratory monitoring. Repeat therapy should be restricted as much as possible and to specific elective cases only. These restrictions must be observed strictly because the possibility of metronidazole developing mutagenic activity cannot be safely excluded and because in animal experiments an increase of the incidence of certain tumours has been noted.

**Hepatotoxicity in patients with Cockayne Syndrome**

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should not be used unless the benefit is considered to outweigh the risk and if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole (see section 4.8).

Prolonged therapy with metronidazole may be associated with bone marrow depression, leading to an impairment of haematopoiesis. Manifestations see section 4.8.

Blood cell counts should be carefully monitored during prolonged therapy.

Special warnings / precautions regarding excipients

This medicinal product contains 14 mmol (or 322 mg) sodium per 100 ml, equivalent to 16% of the WHO recommended maximum daily intake of 2g sodium for an adult.

Interference with laboratory tests
Metronidazole interferes with the enzymatic-spectrophotometric determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase resulting in decreased values (possibly down to zero). Metronidazole has a high absorbance at the wavelength at which nicotinamide-adenine dinucleotide (NADH) is determined. Therefore elevated liver enzyme concentrations may be masked by metronidazole when measured by continuous-flow methods based on endpoint decrease in reduced NADH. Unusually low liver enzyme concentrations, including zero values, have been reported.

### 4.5 Interactions with other medicinal products and other forms of interaction

**Interactions with other medicinal products**

*Amiodarone*
QT interval prolongation and torsade de pointes have been reported with the coadministration of metronidazole and amiodarone. It may be appropriate to monitor QT interval on the ECG if amiodarone is used in combination with metronidazole. Patients treated on an outpatient basis should be advised to seek medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, palpitations, or syncope.

*Busulfan*
Coadministration with metronidazole may significantly increase the plasma concentrations of busulfan. The mechanism of interaction has not been described. Due to the potential for severe toxicity and mortality associated with elevated busulfan plasma levels, concomitant use with metronidazole should be avoided.

*Cimetidine*
Concurrently administered cimetidine may reduce the elimination of metronidazole in isolated cases and subsequently lead to increased metronidazole concentrations in serum.

*Contraceptive drugs*
Some antibiotics can, in some exceptional cases, decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and hereby reduce the re-absorption of unconjugated steroid. Therefore the plasma levels of the active steroid decrease. This unusual interaction can occur in women with a high excretion of steroid conjugates through the bile. There are case reports of oral contraceptive failure in association with different antibiotics, e.g. ampicillin, amoxicillin, tetracyclines and also metronidazole.

*Coumarin derivatives*
Concomitant treatment with metronidazole may potentiate the anticoagulant effect of these and increase the risk for bleeding as a consequence of decreased hepatic degradation. Dose adjustment of the anticoagulant can be necessary.

Concomitant use of metronidazole and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporine, carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels. Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.

*Disulfiram*
Simultaneous administration of disulfiram may cause states of confusion or even psychotic reactions. Combination of both agents must be avoided.

*Fluorouracil*
Metronidazole inhibits the metabolism of concurrently administered fluorouracil, i.e. the plasma concentration of fluorouracil is increased.

*Lithium*
Caution is to be exercised when metronidazole is administered simultaneously with lithium salts, because under metronidazole therapy raised serum concentrations of lithium have been observed.

*Mycophenolate mofetil*
Substances that alter the gastrointestinal flora (e.g., antibiotics) may reduce the oral bioavailability of mycophenolic acid products. Close clinical and laboratory monitoring for evidence of diminished immunosuppressive effect of mycophenolic acid is recommended during concomitant therapy with anti-infective agents.

Phenytoin, barbiturates (phenobarbital): concomitant administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole and therefore decrease its efficacy.

**Other forms of interaction**

*Alcohol*
Intake of alcoholic beverages must be avoided during metronidazole therapy since adverse reactions such as dizziness and vomiting may occur (disulfiram-like effect).

### 4.6 Fertility, pregnancy and lactation

*Contraception in males and females*
See section 4.5 'contraceptive drugs'

*Pregnancy*
The safety of the use of metronidazole during pregnancy has not sufficiently been demonstrated. In particular, reports on the use during early pregnancy are contradictory. Some studies indicated an increased rate of malformations. In animal experiments metronidazole did not show teratogenic effects (see section 5.3).
During the first trimester, Metronidazole Intravenous Infusion 500 mg should only be used to treat severe life-threatening infections, if there is no safer alternative. During the second and third trimester, Metronidazole Intravenous Infusion 500 mg may also be used to treat other infections if its expected benefits clearly outweigh any possible risk.

*Breast-feeding*
Since metronidazole is secreted into breastmilk, nursing is to be interrupted during therapy. Also after the end of the therapy with metronidazole, nursing should not be resumed before another 2 – 3 days because of the prolonged half-life period of metronidazole.

*Fertility*
Animal studies only indicate a potential negative influence of metronidazole on the male reproductive system if high doses lying well above the maximum recommended dose for humans were administered.

### 4.7 Effects on ability to drive and use machines

Even when used as directed, metronidazole may alter reactivity so far that the ability to drive or to use machinery is impaired. This holds true to still a higher degree at the beginning of treatment or in combination with alcohol intake.

### 4.8 Undesirable effects

Undesirable effects are mainly associated with prolonged use or high doses. The most commonly observed effects include nausea, abnormal taste sensations and the risk of neuropathy in case of long term treatment.

In the following listing, for the description of the frequencies of undesirable effects the following terms are used:

| | |
|---|---|
| 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: | (Frequency cannot be estimated from the available data) |

*Infections and infestations*

| | |
|---|---|
| Common: | Superinfections with candida (e.g. genital infections) |
| Rare: | Pseudomembranous colitis, which may occur during or after therapy, manifesting as severe persistent diarrhoea. Details regarding emergency treatment see section 4.4. |

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*Blood and lymphatic system disorders*
Very rare: During therapy with metronidazole, decreases of leukocyte and platelet counts ( granulocytopenia, agranulocytosis, pancytopenia and thrombocytopenia)
Not known: Leucopenia, aplastic anaemia.
During prolonged administration regular monitoring of blood cell counts is mandatory.

*Immune system disorders*
Rare:
- Severe acute systemic hypersensitivity reactions: anaphylaxis, up to anaphylactic shock.
- Severe skin reactions, see *"Skin and subcutaneous disorders"* below.

**These severe reactions demand immediate therapeutic intervention.**

Not known: Mild to moderate hypersensitivity reactions, e. g. skin reactions (see *"Skin and subcutaneous disorders"* below) angioedema.

*Metabolism and nutrition disorders*
Not known: Anorexia

*Psychiatric disorders*
Very rare: Psychotic disorders, including states of confusion, hallucination
Not known: Depression

*Nervous system disorders*
Very rare: Encephalopathy, headache, fever, drowsiness, dizziness, disturbances in sight and movement, vertigo, ataxia, dysarthria, convulsions.
Not known:
- Somnolence or insomnia, myoclonus, seizures, peripheral neuropathy manifesting as paraesthesia, pain, furry sensation, and tingling in the extremities
- Aseptic meningitis

If seizures or signs of peripheral neuropathy or encephalopathy appear, the attending doctor should be informed immediately.

*Eye disorders*
Very rare: Disturbance of vision, e.g. diplopia, myopia.
Not known: Oculogyric crisis, optic neuropathy/neuritis (isolated cases)

*Cardiac disorders*
Rare: ECG changes like flattening of T-wave

*Gastro-intestinal disorders*
Not known: Vomiting, nausea, diarrhoea, glossitis and stomatitis, eructation with bitter taste, epigastric pressure, metallic taste, furred tongue.
Dysphagia (caused by central nervous effects of metronidazole), pancreatitis

*Hepatobiliary disorders*
Very rare: • Abnormal values of hepatic enzymes and bilirubin
Not known: • Hepatitis, jaundice

*Skin and subcutaneous tissue disorders*
Very rare: Allergic skin reactions, e. g. pruritus, urticaria
STEVENS-JOHNSON syndrome, toxic epidermal necrolysis (isolated reports)
**The two latter reactions demand immediate therapeutic intervention**
Not known: *erythema multiforme*

*Musculoskeletal and connective tissue disorders*
Very rare: Arthralgia, myalgia

*Renal and urinary disorders*
Uncommon: Dark coloured urine (due to a metabolite of metronidazole)

*General disorders and administration site conditions*
Not known: Vein irritations (up to thrombophlebitis) after intravenous administration states of weakness, fever

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

**Paediatric population**
Frequency, type and severity of adverse reactions in children are the same as in adults.

### 4.9 Overdose
*Symptoms*
As signs and symptoms of overdose the undesirable effects described under section 4.8 may appear.

*Treatment*
There is no specific treatment or antidote that can be applied in the case of gross overdose of metronidazole. If required, metronidazole can be effectively eliminated by haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Anti-infectives for systemic use – imidazole derivatives
ATC Code: J01X D01

*Mechanism of action*
Metronidazole itself is ineffective. It is a stable compound able to penetrate into microorganisms. Under anaerobic conditions nitroso radicals acting on DNA are formed from metronidazole by the microbial pyruvate-ferredoxin-oxidoreductase, with oxidation of ferredoxin and flavodoxin. Nitroso radicals form adducts with base pairs of the DNA, thus leading to breaking of the DNA chain and consecutively to cell death.

*PK/PD relationship*
The efficacy of metronidazole mainly depends on the quotient of the maximum serum concentration ($c_{max}$) and the minimum inhibitory concentration (MIC) relevant for the microorganism concerned.

*Breakpoints*
For the testing of metronidazole usual dilution series are applied. The following minimum inhibitory concentration have been established to distinguish susceptible from resistant microorganisms:
EUCAST *(European Committee on Antimicrobial Susceptibility Testing)* breakpoints separating susceptible (S) from resistant organisms (R) are as follows:

Gram-positive anaerobes (S: ≤ 4 mg/l R > 4 mg/l)
Gram-negative anaerobes (S: ≤ 4 mg/l R > 4 mg/l)

*List of susceptible and resistant organisms.*
Source: Zentralstelle für die Auswertung von Resistenzdaten (Z.A.R.S.) bei systemisch wirkenden Antibiotika, Germany, January 2011

| **Commonly susceptible species** |
|---|
| **Anaerobes** |
| *Bacteroides fragilis* |
| *Clostridium difficile*° |
| *Clostridium perfringens*°Δ |
| *Fusobacterium* spp.° |
| *Peptoniphilus* spp.° |
| *Peptostreptococcus* spp.° |
| *Porphyromonas* spp.° |
| *Prevotella* spp. |
| *Veillonella* spp.° |
| **Other micro-organisms** |
| *Entamoeba histolytica*° |
| *Gardnerella vaginalis*° |
| *Giardia lamblia*° |
| *Trichomonas vaginalis*° |

| **Species for which acquired resistance may be a problem** |
|---|
| **Gram-negative aerobes** |
| *Helicobacter pylori* |

| **Inherently resistant organisms** |
|---|
| All obligate aerobes |
| **Gram-positive micro-organisms** |
| *Enterococcus* spp. |
| *Staphylococcus* spp. |
| *Streptococcus* spp. |
| **Gram-negative micro-organisms** |
| *Enterobacteriaceae* |
| *Haemophilus* spp. |

° At the time of publication of these tables, no up-to-date data were available. In primary literature, standard reference books and therapy recommendations susceptibility of the respective strains is assumed.
Δ Only to be used in patients with allergy to penicillin

*Mechanisms of resistance to metronidazole*
The mechanisms of metronidazole resistance are still understood only in part.
In *H.pylori* resistance to metronidazole is caused by mutations of a gene that encodes NADPH nitroreductase. These mutations lead to an exchange of amino acids, rendering the enzyme inactive. Thus the step of activation of metronidazole to the active nitroso radical does not take place.
Strains of *Bacteroides* being resistant to metronidazole possess genes encoding nitroimidazole reductases converting nitroimidazoles to aminoimidazoles. Therefore the formation of the antibacterially effective nitroso radicals is inhibited.
There is full cross resistance between metronidazole and the other nitroimidazole derivatives (tinidazole, ornidazole, nimorazole).
The prevalence of acquired resistance of individual species may vary, depending on region and time. Therefore especially for the adequate treatment of severe infections specific local information regarding resistance should be available. If there is doubt about the efficacy of metronidazole due to the local resistance situation, expert advice should be sought. Especially in the case of severe infections or failure of treatment, microbiological diagnosis including determination of species of the microorganism and its susceptibility to metronidazole is required.

### 5.2 Pharmacokinetic properties
*Absorption:*
Since Metronidazole Intravenous Infusion 500 mg is infused intravenously the bioavailability is 100%.

*Distribution:*
Metronidazole is widely distributed in body tissues after injection. Metronidazole appears in most body tissues and fluids including bile, bone, cerebral abscess, cerebro-spinal fluid, liver, saliva, seminal fluid, and vaginal secretions, and achieves concentrations similar to those in plasma. It also diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum. Protein binding is less than 20 %, the apparent volume of distribution is 36 litres.

*Biotransformation:*
Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. Its metabolites include an acid oxidation product, a hydroxy derivative and glucuronide. The major metabolite in the serum is the hydroxylated metabolite, the major metabolite in the urine is the acid metabolite.

*Elimination:*
Approximately 80% of the substance is excreted in urine with less than 10% in the form of the unchanged drug substance. Small quantities are excreted via the liver. Elimination half-life is 8 (6-10) hours.

*Paediatric population*
See section 4.2.

*Characteristics in special patient groups:*
Renal insufficiency delays excretion only to an unimportant degree.
Delayed plasma clearance and prolonged serum half-life (up to 30 h) is to be expected in severe liver disease.

### 5.3 Preclinical safety data
*Repeated dose toxicity*
In dogs, toxic effects after repeated administration appeared in the form of ataxia and tremor. In investigations in monkeys a dose-dependent increase of hepatocellular degeneration was demonstrated after administration over one year.

*Mutagenic and tumorigenic potential*
Metronidazole has a mutagenic effect in bacteria after nitroreduction. Methodologically valid investigations did not give any findings suggesting a mutagenic effect on mammalian cells *in vitro* and *in vivo*. Investigations on lymphocytes of patients treated with metronidazole did not give any relevant finding indicating DNA damaging effects.

There are findings suggesting a tumorigenic effect on rats and mice. Of note, there was an increased rate of lung tumours in mice after oral administration. This, however, does not seem to be due to a genotoxic mechanism, because no increased mutation rates have been found in various organs, including lungs, in transgenic mice after high metronidazole doses.

*Reproduction toxicity*
No teratogenic or other embryotoxic effects have been observed in investigations with rats and rabbits.

After repeated administration of metronidazole over 26 – 80 weeks to rats, testicular and prostatic dystrophy has only been observed with high doses.

Metronidazole has been shown to be non-mutagenic in mammalian cells in vitro and in vivo.

Metronidazole and a metabolite have been shown to be mutagenic is some tests with non mammalian cells.

Although Metronidazole has been shown to be carcinogenic in certain species of mice, it was not carcinogenic in either rats or guinea pigs. There is no suspicion of carcinogenicity in man.

Daily peroral metronidazole at 5-times the maximum human daily dose for greater than 4 weeks caused testicular toxicity and infertility in male rats. Fertility was restored in most subjects by 8 weeks after cessation of treatment, whereas the lower testicular and epididymal weights and sperm counts had improved but were still observed.

Daily peroral metronidazole at approximately 6-times the maximum human daily dose for ≥2 weeks caused testicular toxicity in male mice. Most indices of testicular toxicity were restored within 2 months after cessation of treatment, whereas the lower testicular and epididymal weights had improved but were still observed.

These studies demonstrate that the adverse effects of metronidazole on the male reproductive system are wholly or partially reversible after treatment withdrawal (see section 4.6).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Sodium chloride,
Disodium phosphate dodecahydrate,
Citric acid monohydrate,
Water for injections

### 6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except mentioned in section 6.6.

### 6.3 Shelf life
**Unopened**
3 years.

**after first opening the container**
Unused contents must be discarded and not be stored for later use.

**after dilution according to directions**
From a microbiological point of view, dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ° C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage
Do not store above 30 °C.

Keep the container in the outer carton in order to protect from light.
Storage conditions for diluted medicinal product see section 6.3.

### 6.5 Nature and contents of container
The product is supplied in:
– bottles of low-density polyethylene, contents: 100 ml

### 6.6 Special precautions for disposal and other handling
No special requirements

*Other handling instructions:*
For single use only. Discard container and any unused contents after use.

The product can be diluted in sodium chloride 0.9 % w/v or glucose 5 % w/v solutions for infusion. For dilution procedures the usual precautions of asepsis must be adhered to.

Only to be used if solution is clear and slightly yellow and the container and its closure do not show visible signs of damage.

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Manufactured by:
**B. Braun Medical Industries Sdn. Bhd.**
11900 Bayan Lepas, Penang, Malaysia.