For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

MACROTOR SUSPENSION

1. Generic Name

Azithromycin oral suspension I.P.100mg/5ml & 200mg/5ml

2. Qualitative and quantitative Composition:

MACROTOR SUSPENSION 100

Composition:

Each 5ml contains

Azithromycin I.P. (As dihydrate)

Equivalent to Azithromycin anhydrous……..100mg

Colour: Quinoline yellow WS

Flavoured syrupy base……..q.s.

MACROTOR SUSPENSION 200

Each 5 ml contains:

Azithromycin I.P. (As dihydrate)

Equivalent to Azithromycin anhydrous……..200mg

Colour: Quinoline yellow WS

Flavoured syrupy base……q.s.

3. Dosage form and strength

Dosage form: powder

Strength: 100mg/5ml & 200mg/5ml/

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin

- Upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis
- Acute otitis media
- Lower respiratory tract infections: acute bronchitis and mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

Considerations should be given to official guidance on the appropriate use of antibacterial agents. Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

4.2 Posology and method of administration

Adults

In uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000 mg in one single oral dose.

For all other indications the dosage is 1500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dosage (1500 mg) can also be given over a period of 5 days with 500 mg on the first day and then 250 mg on days 2 to 5.

To treat these patients other pharmaceutical forms are also available.

Elderly

In the elderly the same dosage as for adults can be given.

Children and adolescents (< 18 years)

The total dosage in children aged 1 year and older is 30 mg/kg administered as 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days, according to the tables shown below. There are limited data on use in children younger than 1 year.

Weight (kg)	3 Day therapy	5-day therapy		Contents of the bottle
	Day 1-3	10 mg/kg/day	Day 1	
10kg	2.5ml	2.5ml	1.25ml	15ml
12kg	3ml	3ml	1.5ml	15ml
14kg	3.5ml	3.5ml	1.75ml	15ml
16kg	4ml	4ml	2ml	15ml
17 – 25 kg	5ml	5ml	2.5ml	15ml
26 – 35 kg	7.5ml	7.5ml	3.75ml	22.5ml
36 – 45 kg	10ml	10ml	5ml	30ml
> 45 kg	12.5 ml	12.5 ml	6.25ml	22.5 ml + 15 ml

The dosage for the treatment of pharyngitis caused by Streptococcus pyogenes is an exception: in the treatment of pharyngitis caused by Streptococcus pyogenes Azithromycin has proved to be effective when it is administered to children as a single dose of 10 mg/kg or 20 mg/kg for 3 days with a maximum daily dosage of 500 mg. At these two dosages a comparable clinical effect was observed, even if the eradication of the bacteria was more significant at a daily dosage of 20 mg/kg. Penicillin is however the drug of first choice in the treatment of pharyngitis caused by Streptococcus pyogenes and the prevention of subsequent rheumatic fever.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min)

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Method of administration

Before use the powder should be reconstituted with water into a white to off white coloured, homogenous suspension. After reconstitution the drug can be administered using a PE/PP syringe for oral use.

After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. Azithromycin powder for oral suspension should be given in a single daily dosage. The suspension may be taken together with food.

4.3 Contraindications

Hypersensitivity to azithromycin, to other macrolide antibiotics, or to any of the excipients.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

As is true of all antibiotics, it is advisable to be alert to signs of superinfection by non- sensitive micro-organisms including fungi.

Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should also be considered in patients who get diarrhoea after starting treatment with azithromycin.

There is no experience of the safety and effectiveness of long-term use of azithromycin in the above-mentioned indications. In the event of quickly recurring infections, just as is the case with other antibiotics, treatment with another antibacterial drug should be considered. Due to the theoretical possibility of ergotism, azithromycin and ergotamine derivatives should not be given at the same time.

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation. Therefore azithromycin should not be used:

- In patients with congenital or documented acquired QT prolongation.
- With other active substances that prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- In patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- In patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

The following should be considered before prescribing azithromycin:

Azithromycin powder for oral suspension is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

As for other macrolides, high resistance rates of Streptococcus pneumoniae (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by Streptococcus pneumoniae.

<u>Pharyngitis/ tonsillitis</u>

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by T. palladium should be excluded.

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

Use in renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10–80 ml/min). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) as systemic exposure may be increased

Use in hepatic impairment

Since azithromycin is metabolised in the liver and excreted in the bile, the medicinal product should not be given to patients suffering from severe liver disease. No studies have been conducted regarding the treatment of such patients with azithromycin. When severe liver impairment occurs, the treatment with azithromycin should be ceased.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine since it contains sucrose.

4.5 Drugs interactions

Theophylline

Pharmacokinetic research has shown no interaction between azithromycin and theophylline on co-administration to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

Oral coumarin-type anticoagulants

In pharmacokinetic research in healthy volunteers, azithromycin did not alter the anticoagulant effect of one dose of 15 mg warfarin. There are reports of enhanced anticoagulation in co-administration of azithromycin with oral coumarin-type anticoagulants. Although a causal connection has not been established, attention should be paid to the frequency of measurement of the prothrombin time.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was seen on the pharmacokinetics of carbamazepine or the active metabolite of carbamazepine.

Ergotamine derivatives

In patients who are being treated with ergotamine derivatives, ergotism may be induced by co-administration of some macrolide antibiotics. There are no known data on a possible interaction between ergotamine derivatives and azithromycin. As there is a theoretical possibility of ergotism, azithromycin and ergotamine derivatives should not be combined.

Ciclosporin

On the basis of limited pharmacokinetic data on interaction between azithromycin and ciclosporin in healthy volunteers, caution should be exercised in concurrent administration of these medicinal products. If concurrent administration is necessary, the ciclosporin levels must be checked and if necessary the ciclosporin dosage adjusted.

Digoxin

It is known that some macrolide antibiotics limit the metabolism of digoxin in the bowel. In patients who are treated concurrently with azithromycin and digoxin, account should be taken of potentially raised digoxin levels and these levels must be monitored.

Antacids

In a pharmacokinetic study into the effect of concurrent administration of antacids and azithromycin, no effect was seen on the total biological availability, although peak serum levels were reduced by 30%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

Cimetidine

A single dose of cimetidine administered 2 hours before azithromycin had no effect on the pharmacokinetics of azithromycin.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was seen on the pharmacokinetics of methylprednisolone.

Zidovudine

Single doses of 1000 mg azithromycin and multiple doses of 600 mg or 1200 mg Azithromycin had no effect on the plasma pharmacokinetics or the renal excretion of zidovudine or its glucuronide metabolite. However, on administration of azithromycin the concentration of phosphorylated zidovudine, the clinically active metabolite, increased in the peripheral mononuclear blood cells. The clinical significance of this finding is still unclear, but may possibly be an advantage for patients.

Terfenadine

Azithromycin has no effect on the pharmacokinetics of terfenadine, given every 12 hours at the recommended dosage of 60 mg.

Addition of azithromycin did not result in a significant change of cardiac repolarization (QT interval), measured at a steady state dosage of terfenadine.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Didanosine

On comparison with a placebo in 6 test subjects, daily doses of 1200 mg azithromycin with didanosine appeared to have no effect on the pharmacokinetics of didanosine.

Rifabutin

Concurrent administration of azithromycin and rifabutin had no effect on the serum concentration of either medicinal product.

Neutropenia was seen in patients who were given simultaneous treatment with azithromycin and rifabutin. In spite of the fact that neutropenia has been associated with the use of rifabutin, no causal connection with the combination with Azithromycin could be established. Astemizole, triazolam, midazolam, alfentanil

There are no known data on interactions with astemizole, triazolam, midazolam or alfentanil. Caution is advised in the coadministration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Nelfinavir

Concomitant administration of 1200 mg azithromycin and steady state nelfinavir (750 mg 3 times daily) resulted in on average 16% decrease of nelfinavir AUC, an increase of azithromycin AUC and C_{max} with 113% and 136% respectively. No dose adjustment is necessary but patients should be monitored for known side effects of azithromycin

4.6 Use in special populations

NA

4.7 Effects on ability to drive and use machines

NA

4.8 Undesirable effects

In this section undesirable effects are defined as follows:

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).

Within each frequency group, undesirable effects are listed in order of decreasing seriousness.

Cardiac disorders

Rare: Palpitations, arrhythmia (including ventricular tachycardia).

There is a potential risk of QT lengthening and torsades in predisposed patients

Blood and lymphatic system disorders

Rare: Thrombocytopenia, haemolytic anaemia and transient episodes of mild neutropenia have been observed in clinical research. No causal connection with the use of azithromycin could be established for this.

Nervous system disorders

Uncommon: Dizziness, convulsions, headache, somnolence, changes in smell and/or taste. Rare: Paresthesia, syncope, insomnia, hyperactivity.

Ear and labyrinth disorders

Rare: Loss of hearing including deafness and/or tinnitus has been reported in long-term use of high doses of azithromycin during clinical research. In those cases where follow-up data were available, the majority of these undesirable effects proved to be reversible.

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, gastrointestinal symptoms (pain/cramps).

Uncommon: Very watery faeces (as a consequence of infrequent dehydration of the system), flatulence, digestive disturbances.

Rare: Constipation, discolouration of the tongue, pancreatitis. Discolouration of the teeth and pseudomembranous colitis have been reported.

Renal and urinary disorders

Rare: Interstitial nephritis, acute renal failure.

Skin and subcutaneous tissue disorders

Uncommon: Allergic reactions including skin rash and pruritis.

Rare: Allergic reactions including angio-oedema, urticaria, photosensitivity. Serious skin reactions including erythema multiforme, Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia.

Metabolism and nutrition disorders

Uncommon: Anorexia.

Infections and infestations

Uncommon: Vaginitis.

Rare: Candidiasis.

Vascular disorders

Rare: Hypotension.

General disorders and administration site conditions

Rare: Asthenia, fatigue, malaise

Immune system disorders

Rare: Anaphylaxis, including oedema (rarely fatal)

Hepatobiliary disorders

Rare: Abnormal liver function, including hepatitis and cholestatic jaundice have been reported, as also have rare cases of hepatic necrosis and liver failure, which in rare cases, have resulted in death.

Psychiatric disorders

Rare: Aggressive reactions, restlessness, anxiety, nervousness, depersonalization, in older patients delirium can occur

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

The symptoms that occurred at higher than recommended dosages were equivalent to known undesirable effects at normal dosage. Characteristic symptoms of overdose with macrolide antibiotics are: reversible loss of hearing, serious nausea, vomiting and diarrhoea. In cases of overdose, gastric lavage and general supportive measures are indicated.

5 Pharmacological properties

5.1 Mechanism of Action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among Streptococcus pneumoniae, betahaemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

According to the CLSI (Clinical and Laboratory Standards Institute) the following breakpoints have been defined for azithromycin:

- susceptible ≤ 2 ng/ml; resistant ≥ 8 ng/ml
- Haemophilus spp.: susceptible ≤ 4 ng/ml

Streptococcus pneumoniae and Streptococcus pyogenes: susceptible ≤ 0.5 Ng/ml; resistant ≥ 2 ng/ml.

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms

Haemophilus influenzae*
Moraxella catarrhalis*
Neisseria gonorrhoeae
Other microorganisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
Mycoplasma pneumonia*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus*
Streptococcus agalactiae
Streptococcus pneumoniae*
Streptococcus pyogenes*
Other microorganisms
Ureaplasma urealyticum
Inherently resistant organisms
Staphylococcus aureus – methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains
Escherichia coli
Pseudomonas aeruginosa

Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications

5.2 Pharmacokinetic properties

Absorption

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma).

This indicates that the substance is bound in the tissues in considerable quantities. Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.

The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

Approximately 12% of an intravenously administered dose of azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged azithromycin were found in human bile. In this, ten metabolites were also detected (formed by N- and O-desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and microbiological assessment methods shows that the metabolites are microbiologically inactive.

In animal models high concentrations of azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of azithromycin are released than during inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of azithromycin in infectious tissue.

Pharmacokinetics in Special Populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension.. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than adults with 224ug/l in children aged 0.6-5 years and after 3 days dosing and 383ug/l in those aged 6-15 years. The t1/2 of 36 h in the older children was within the expected range for adults.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule no true toxicological consequences were observed which were associated with this. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Reproductive toxicity:

In embryotoxicity studies in mice and rats no teratogenic effects were observed. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to slight retardations in fetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, slight retardations in physical development and delay in reflex development were observed following treatment with 50 mg/kg/day azithromycin and above.

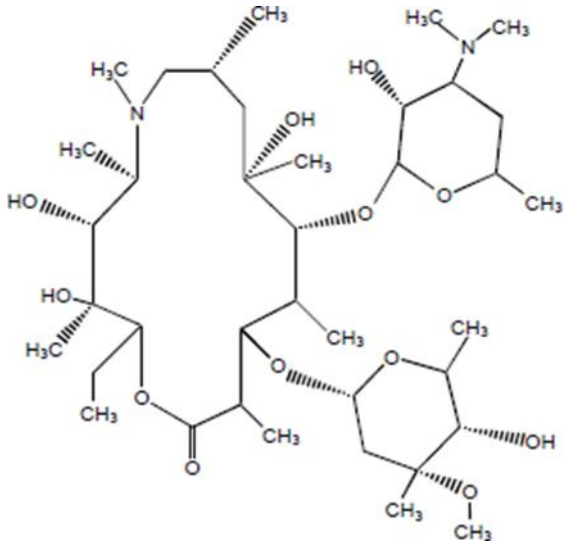
7 Description

Azithromycin:

Azithromycin (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-alfa-L-ribo-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3(dimethylamino)-Beta-D-xylo hexopyranosyl]-1-oxa-6-azacyclopentadecan-15-one.

Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00.

Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

MACROTOR SUSPENSION 100, MACROTOR SUSPENSION 200 is available in 15ml bottle.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°c, protected from moisture.

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Date of revision

JUN 22

11. MARKETED BY

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IN/PMACROTOR SUSPENSION/JUN 22/02/PI