Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pivmecillinam hydrochloride Karo Pharma 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg Pivmecillinam hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

A white capsule-shaped, film-coated tablet, size 8 x 17 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pivmecillinam hydrochloride Karo Pharma is indicated for adults in the treatment of acute uncomplicated cystitis caused by bacteria sensitive to mecillinam (see section 5.1).

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

4.2 Posology and method of administration

Posology
Adults: 400 mg, 3 times daily.

Duration of treatment
Recommended treatment duration is 3 days.

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

Paediatric population
Pivmecillinam hydrochloride Karo Pharma should not be used in children and adolescents below 18 years because the efficacy and safety have not yet been established.

Elderly population
Renal excretion of mecillinam is delayed in the elderly, but significant accumulation of the drug is not likely at the recommended adult dosage of Pivmecillinam hydrochloride Karo Pharma. Dosage adjustment is not necessary.

Renal impairment
Renal excretion of mecillinam is delayed in patients with reduced kidney function, but significant accumulation of the drug is not likely at the recommended adult dosage of Pivmecillinam hydrochloride Karo Pharma. Dosage adjustment is not necessary (see section 5.2).

Hepatic impairment
Dosage adjustment is not necessary.

Method of administration
Pivmecillinam hydrochloride Karo Pharma must be taken with at least half a glass of liquid. Pivmecillinam hydrochloride Karo Pharma may be taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Hypersensitivity to penicillins or cephalosporins.
- Any conditions resulting in impaired transit through the oesophagus.
- Genetic metabolism anomalies known to be leading to severe carnitine deficiency such as carnitine transporter defect, methylmalonic aciduria and propionic acidaemia.

4.4 Special warnings and precautions for use

- Pseudomembranous colitis caused by *Clostridium difficile* may occur. If diarrhoea occurs after use, the possibility of pseudomembranous colitis should be considered, and appropriate precaution should be taken.
- Should not be used by patients suffering from porphyria as pivmecillinam has been connected to acute attacks of porphyria.
- Concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided due to increased risk of carnitine depletion.
- Pivmecillinam hydrochloride Karo Pharma film-coated tablets should be used with caution for long-term or frequently-repeated treatment, due to the possibility of carnitine depletion. Symptoms of carnitine depletion include muscle aches, fatigue, and confusion.
- Interference with neonatal screening tests: The intake of pivmecillinam shortly before delivery may cause a false positive test for isovaleric acidemia in the newborn as part of neonatal screening. This may be due to the formation of pivaloylcarnitine simulating the presence of isovalerylcarnitine. It is therefore recommended to include a second tier screening test for each sample obtained from newborns tested positive for isovaleric acidaemia if those findings are suspected of being pivmecillinam-related false positive (see section 4.6).
- The tablets must be taken with at least half a glass of fluid due to the risk of oesophageal ulceration.

4.5 Interaction with other medicinal products and other forms of interaction

- Simultaneous administration of probenecid reduces the excretion of mecillinam and hence increases the blood level of the antibiotic.
- Clearance of methotrexate from the body can be reduced by concurrent use of penicillins
- Concurrent treatment with valproic acid, valproate or other medication liberating pivalic acid should be avoided due to increased risk of carnitine depletion.
- The bactericidal effect of mecillinam may be hindered by concurrent administration of products with bacteriostatic effect, for instance erythromycin and tetracyclines.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no malformative nor feto/neonatal toxicity of pivmecillinam/mecillinam. Pivmecillinam hydrochloride Karo Pharma can be used during pregnancy if clinically needed.
Some cases of false-positive newborn screening tests simulating the presence of isovaleric acidaemia have been reported. The intake of pivmecillinam shortly before delivery may cause a false positive test for isovaleric acidaemia in the newborn as part of neonatal screening (see section 4.4).

Breastfeeding
Mecillinam is excreted in human milk, but at therapeutic doses of Pivmecillinam hydrochloride Karo Pharma no effects on the breast-fed newborns/infants are anticipated. Pivmecillinam hydrochloride Karo Pharma can be used during breast-feeding.

Fertility
There are no clinical studies with Pivmecillinam hydrochloride Karo Pharma regarding fertility. A pre-clinical study did not show an effect on fertility in rats.

4.7 Effects on ability to drive and use machines

Pivmecillinam hydrochloride Karo Pharma has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The estimation of the frequency of undesirable effects is based on an analysis of pooled data from clinical studies and spontaneous reporting.

The most frequently reported adverse reactions are nausea and diarrhoea.

Anaphylactic reactions and fatal pseudomembranous colitis (see section 4.4) have been reported.

Undesirable effects are listed by MedDRA SOC and the individual undesirable effects are listed starting with the most frequently reported. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

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)

Infections and infestations	
Common:	Vulvovaginal mycotic infection
Uncommon:	*Clostridium difficile* colitis
Blood and lymphatic system disorders	
Uncommon:	Thrombocytopenia
Immune system disorders	
Uncommon:	Anaphylactic reaction
Not known:	Anaphylactic shock
Metabolism and nutrition disorders	
Uncommon:	Carnitine decreased
Nervous system disorders	
Uncommon:	Headache Dizziness
Ear and labyrinth disorders	
Uncommon:	Vertigo
Gastrointestinal disorders	
Common	Diarrhoea Nausea
Uncommon:	Vomiting Abdominal pain Dyspepsia Oesophageal ulcer Oesophagitis Mouth ulceration
Hepatobiliary disorders	
Uncommon:	Hepatic function abnormal
Skin and subcutaneous tissue disorders	
Uncommon:	Rash* Urticaria Pruritus
Not known:	Angioedema
General disorders and administration site conditions	
Uncommon:	Fatigue

*Various types of rash reactions such as erythematous, macular or maculo-papular skin reactions have been reported

Class adverse reactions of beta-lactam antibiotics

- Slight reversible increase in aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase, and bilirubin
- Neutropenia
- Eosinophilia

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults, based on limited data.

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There is no experience of overdose with Pivmecillinam hydrochloride Karo Pharma. However, excessive doses of Pivmecillinam hydrochloride Karo Pharma are likely to induce nausea, vomiting, abdominal pain and diarrhoea. Treatment should be restricted to symptomatic and supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, penicillins with extended spectrum.
ATC code: J01CA08

Mechanism of action
Pivmecillinam hydrochloride Karo Pharma is an orally active antibiotic, containing the pro-drug pivmecillinam. This is the pivaloyloxymethylester of the amidinopenicillanic acid, mecillinam. On oral administration, pivmecillinam is well absorbed and subsequently hydrolysed in the body to mecillinam, the active antibacterial agent, by non-specific esterases present in blood, gastro-intestinal mucosa and other tissues. Mecillinam is a beta-lactam with a narrow-spectrum of activity. It is mainly active against Gram-negative bacteria and works by interfering with the biosynthesis of the bacterial cell wall.

Mecillinam exerts high specificity against penicillin-binding protein 2 (PBP-2) in the Gram-negative cell wall, unlike the majority of other beta-lactam agents, which preferentially bind Gram-negative PBP-1A, -1B or -3. Synergy has been observed when mecillinam is combined with other beta-lactam antibiotics, including ampicillin, amoxicillin, cefoxitin, cefalotin, cefazolin, cefradine, cefamandole, ceftazidime and ceftriaxone, against selected isolates of most Enterobacteriaceae.

Pivmecillinam hydrochloride Karo Pharma has low impact on the normal skin, oral, intestinal and vaginal microflora.

Resistance
As a narrow-spectrum antibiotic active against Gram-negative bacilli, pivmecillinam is unlikely to contribute to the widespread of resistant bacterial strains. The exclusive action of pivmecillinam on PBP-2 results in the low cross-resistance with other beta-lactams (penicillins and cephalosporins). Mecillinam has limited susceptibility to most of the beta-lactamases (including ESBL) produced by Enterobacteriaceae.

In Enterobacteriaceae, resistance to mecillinam may be due to marked production of some beta-lactamases and modification of penicillin binding proteins.

Susceptibility testing breakpoints

EUCAST: S ≤8 mg/L / R >8 mg/L (for *E. coli*, *Klebsiella spp*. and *P. mirabilis)*

Generally sensitive species
Gram negative micro-organisms
Enterobacter spp.
Escherichia coli

Klebsiella spp.
Proteus mirabilis

Naturally resistant species
Gram-positive micro-organisms
Enterococcus faecalis
Enterococcus faecium
*Staphylococcus saprophyticus**
Gram negative micro-organisms
Pseudomonas spp.

*Due to the high concentrations of mecillinam in urine, clinical effect is normally obtained in acute uncomplicated cystitis caused by *S. saprophyticus*.

Pharmacokinetic/pharmacodynamic relationship(s)
As a beta-lactam antibiotic, the bacteriological effect of Pivmecillinam hydrochloride Karo Pharma in the treatment of acute uncomplicated cystitis is expected to depend on time above MIC.

Clinical efficacy against specific pathogens
Efficacy has been demonstrated in clinical studies against the pathogens that were susceptible to mecillinam in vitro in the treatment of acute uncomplicated cystitis. Mecillinam is a beta-lactam with a narrow spectrum of activity against Gram-negative bacilli. Mecillinam is highly active against *E. coli, Klebsiella spp, Proteus spp.* and *Enterobacter spp*. The *S. saprophyticus*, which exhibits borderline susceptibility in vitro, is susceptible in vivo due to the high concentration of mecillinam excreted in urine.

5.2 Pharmacokinetic properties

Absorption, Distribution, Biotransformation
Pivmecillinam hydrochloride is the pro-drug of mecillinam, that is hydrolysed in the body to mecillinam, the active antibacterial agent (see section 5.1).

Following oral administration of 400 mg pivmecillinam peak concentrations of approximately 3 µg/mL is attained within 1-1½ hours after dosing. The bioavailability of orally administered pivmecillinam is approximately 60-70% . Bioavailability of Pivmecillinam hydrochloride Karo Pharma tablets is not affected by taking the tablets with food.

Elimination
The elimination half-life of mecillinam is about 1 hour. It is excreted primarily in the urine with some biliary excretion. Mecillinam is to a large extent excreted by the kidneys by filtration and active tubular secretion. Probenecid, which inhibits tubular secretion, also inhibits the elimination of mecillinam. Approximately 60-70% of the mecillinam reaching the systemic circulation is excreted unchanged in urine; almost all within the first 6 hours after dosing resulting in urine concentrations > 200 mg/L after oral administration of one 400 mg tablet.

The elimination of mecillinam is reduced by approximately 75% in patients with severe renal impairment (see section 4.2).

Low concentrations of mecillinam are observed in foetuses, breast milk, and amniotic fluid. The protein binding of mecillinam in human serum is 5-10%.

Linearity/non-linearity
Mecillinam displays linear pharmacokinetics in the clinically relevant range.

Gender differences in the pharmacokinetics of mecillinam have not been reported.

Clinically relevant accumulation of mecillinam does not take place at dosing up to four times daily and there are no indications that the pharmacokinetics change over time during repeated dosing.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or toxicity to reproduction.

No carcinogenicity data are available for pivmecillinam or the active drug mecillinam.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients in the tablet core:

- Cellulose, microcrystalline
- Hydroxypropylcellulose
- Magnesium stearate

Excipients in the film coating:

- Hypromellose 6 cps
- Simethicone emulsion 30%
- Paraffin, synthetic

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC-aluminium blister:
9, 10, 15, or 20 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

KARO PHARMA AB
Box 16184
103 24 Stockholm
Sweden

8 MARKETING AUTHORISATION NUMBER

PA22650/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd December 2016
Date of last renewal: 13th Febuary 2019

10 DATE OF REVISION OF THE TEXT

January 2024