SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
RITMOLL 300 mg Film-Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Propafenone hydrochloride ..... 300 mg

Excipients:
For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
White, biconvex, round, one side notched, film-coated tablet.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
RITMOLL is indicated for the prophylaxis and treatment of symptomatic supraventricular tachyarrhythmias requiring treatment, such as AV node tachycardias, supraventricular tachycardias in patients with Wolff-Parkinson-White (WPW) syndrome or paroxysmal atrial fibrillation, and severe symptomatic ventricular tachyarrhythmias that the physician considers life-threatening.

4.2 Posology and method of administration
It is recommended that RITMOLL therapy be initiated under a hospital conditions and by a physician experienced in the treatment of arrhythmias. The individual maintenance dose should be determined by cardiological monitoring including ECG and blood pressure control. If a >20% prolongation in the QRS interval is detected, the dose should be reduced or the drug should be discontinued until the ECG returns to the normal range.

Oral administration
The dosage should be individually adjusted according to the patient's needs.
In patients with a markedly widened QRS complex or in case of the development of second- or third-degree AV block, dose reduction should be considered.

Adults:
In patients weighing approximately 70 kg, a daily dose of 450–600 mg divided into two or three doses is recommended during the initial titration period and maintenance therapy (from 3x1 RITMOLL 150 mg Film Tablets to 2x1 RITMOLL 300 mg Film Tablets). In some cases, it may be necessary to increase the daily dose to 900 mg (3x1 RITMOLL 300 mg Film Tablet or 3x2 RITMOLL 150 mg Film Tablet).

In patients with lower body weight, daily doses should be reduced accordingly.
Dose escalation should only be performed after three to four days of treatment.

Additional information on special populations

Pediatric population

RITMOLL 150 mg Film Tablet is not suitable for use in children.

Elderly

No overall differences in safety and effectiveness have been observed in this patient population, but greater sensitivity in some elderly individuals cannot be ruled out. Therefore, these patients should be monitored carefully. Treatment should be initiated cautiously with small dose increments.

The same applies to maintenance therapy. Any required dose increase should not be made without a treatment-free period of five to eight days.

Hepatic and/or renal impairment:

Drug accumulation may occur after standard therapeutic doses. In such patients with these conditions, propafenone hydrochloride titration can still be conducted with ECG and clinical monitoring.

Method of administration:

Due to the bitter taste of propafenone and its superficial anesthetic effect, the film tablets should be swallowed without sucking or chewing, with a sufficient amount of liquid after meals.

4.3. Contraindications

Propafenone hydrochloride is contraindicated in the following cases:

- Known hypersensitivity to the active substance propafenone hydrochloride or to any of the ingredients of the medicinal product,
- Known Brugada syndrome,
- Myocardial infarction within the last 3 months,
- Significant structural heart disease,
- Uncontrolled congestive heart failure with a left ventricular flow below 35%,
- Cardiogenic shock (except when caused by arrhythmia),
- Severe symptomatic bradycardia,
- In the absence of an artificial pacemaker: sinus node dysfunction, atrial conduction disorders, second-degree or higher atrioventricular block, bundle branch block or distal block,
- Severe hypotension,
- Significant disturbances in electrolyte balance (e.g., potassium metabolism disorders),
- Severe obstructive pulmonary disease,
- Propafenone hydrochloride may exacerbate myasthenia gravis.
- Patients concomitant using ritonavir (due to the potential for increased plasma concentrations).

4.4. Special warnings and precautions for use

The weak negative inotropic effect of RITMOLL may be significant in patients predisposed to heart failure.

In patients with implanted pacemakers, propafenone therapy may alter the stimulus generation and sensing thresholds of the pacemaker. Therefore, pacemaker function should be monitored during treatment, and reprogramming should be performed if necessary.

There is a potential for conversion of paroxysmal atrial fibrillation to atrial flutter accompanied by 2:1 conduction block or 1:1 conduction (see section 4.8).

Due to its beta-blocking effect, propafenone hydrochloride should be used with caution in patients with obstructive airway conditions such as asthma.

As with other Class 1c antiarrhythmic agents, individuals with significant structural heart disease may be more susceptible to serious adverse events. Therefore, propafenone hydrochloride is contraindicated in these patients (see section 4.3).

In asymptomatic carriers, previously hidden Brugada syndrome may become apparent after use of propafenone, or Brugada-like electrocardiogram (ECG) changes may be triggered. An ECG should be performed after initiation of propafenone treatment to rule out changes suggestive of Brugada syndrome.

Like other antiarrhythmic agents, propafenone can cause proarrhythmic effects, i.e., it may induce new arrhythmias or worsen pre-existing arrhythmias (see section 4.8). It is important that every patient receiving propafenone hydrochloride undergoes electrocardiographic and clinical evaluation before and during treatment in order to determine whether the patient's response to the drug supports continuation of therapy.

4.5. Interaction with other medicinal products and other forms of interaction

The possibility of increased side effects of RITMOLL should be considered when administered concurrently with local anesthetics (e.g., during pacemaker implantation, operations, or dental treatments) or with drugs that reduce heart rate and/or myocardial contractility (e.g., beta-blockers, tricyclic antidepressants).

When propafenone and lidocaine are used concomitantly in patients, no significant effects on their pharmacokinetic properties have been observed. However, concomitant use of propafenone hydrochloride and intravenous lidocaine has been reported to increase the risk of central nervous system side effects associated with lidocaine.

During treatment with propafenone hydrochloride, increases in plasma or blood concentrations of propranolol, metoprolol, desipramine, cyclosporine, theophylline, and digoxin have been reported. If signs of overdose appear, the dosages of these products should be appropriately reduced.

Concurrent use with SSRIs such as fluoxetine and paroxetine may increase plasma levels of propafenone hydrochloride. In rapid metabolizers, co-administration of propafenone hydrochloride with fluoxetine increased the C_{max} and AUC values of S-propafenone by 39% and 50%, respectively, and those of R-propafenone by 71% and 50%, respectively. Lower doses of propafenone may be sufficient to achieve the desired therapeutic response.

In patients receiving oral anticoagulants (e.g., phenprocoumon, warfarin) concurrently, coagulation status should be closely monitored, as propafenone hydrochloride may enhance the effect of these drugs and prolong prothrombin time. If signs of overdose appear, the dosages of these products should be appropriately reduced.

Co-administration of propafenone hydrochloride with drugs metabolized by CYP2D6 (such as venlafaxine) may result in increased blood levels of these drugs.

Drugs that inhibit CYP2D6, CYP1A2, and CYP3A4 enzymes e.g., ketoconazole, cimetidine, quinidine, erythromycin, and grapefruit juice may lead to increased propafenone hydrochloride levels. When propafenone hydrochloride is co-administered with such enzyme inhibitors, patients should be closely monitored and the dosage adjusted as needed.

Combination therapy with amiodarone and propafenone hydrochloride may affect conduction and repolarization and may lead to abnormalities with proarrhythmic potential. Dosage adjustment for both compounds may be necessary depending on the therapeutic response.

Concurrent use of propafenone hydrochloride with phenobarbital and/or rifampicin (CYP3A4 inducers) may reduce the antiarrhythmic effect of propafenone hydrochloride as a result of decreased plasma levels of propafenone. During concomitant chronic use of phenobarbital and/or rifampicin, the response to propafenone hydrochloride therapy should be monitored.

Due to the potential for increased plasma concentrations, the concomitant administration of ritonavir and propafenone hydrochloride is contraindicated (see section 4.3).

Special Populations
Pediatric Population
Interaction studies have only been conducted in adults. It is not known whether the interactions in the pediatric population are similar to those in adults.

4.6. Pregnancy and lactation
Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)
There are no available data.

Pregnancy:
Studies conducted in animals have not shown teratogenic effects; however, there are no adequate and well-controlled studies in pregnant women. Propafenone hydrochloride should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. It is known that propafenone hydrochloride crosses the placental barrier in humans.

The concentration of propafenone in the umbilical cord has been reported to be 30% of that in maternal blood.

Lactation:
It has not been studied whether propafenone is excreted in human milk. Limited data suggest that propafenone may be excreted into breast milk. Propafenone hydrochloride should be used with caution in breastfeeding mothers.

Reproductive ability/Fertility:
There are no available data.

4.7. Effects on ability to drive and use machines
Blurred vision, dizziness, fatigue and postural hypotension may affect the patient's reaction time and impair ability to operate machines or drive vehicles.

4.8. Undesirable effects
Summary of the safety profile
The most commonly observed adverse reactions with propafenone therapy are dizziness, cardiac conduction disorders, and palpitations.

Results from clinical studies or post-marketing surveillance
Table 1 shows the clinical adverse reactions that occurred in at least one of 885 patients who received propafenone hydrochloride SR in five phase II and two phase III studies. Adverse reactions and frequencies are expected to be similar for IR formulations. The table also includes adverse reactions from post-marketing experience with propafenone. Reactions thought to be at least possibly related to propafenone are shown by system organ class and frequency using the following definitions: 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), unknown (frequency cannot be estimated from available data). When the severity could be assessed, adverse reactions are listed in descending order of seriousness within each frequency group.

Blood and lymphatic system disorders
Uncommon: Thrombocytopenia
Unknown: Agranulocytosis, leukopenia, granulocytopenia

Immune system disorders
Unknown: Hypersensitivity[1]

Metabolism and nutrition disorders
Uncommon: Decreased appetite

Psychiatric disorders
Common: Anxiety, sleep disorders
Uncommon: Nightmares
Unknown: Confusion

Nervous system disorders
Very common: Dizziness[2]
Common: Headache, dysgeusia
Uncommon: Syncope, ataxia, paresthesia
Unknown: Convulsion, extrapyramidal symptoms, restlessness

Eye disorders
Common: Blurred vision

Ear and labyrinth disorders
Uncommon: Vertigo

Cardiac disorders
Very common: Cardiac conduction disorders[3], palpitations
Common: Sinus bradycardia, bradycardia, tachycardia, atrial flutter
Uncommon: Ventricular tachycardia, arrhythmia[4]
Unknown: Ventricular fibrillation, heart failure[5], decreased heart rate

Vascular disorders
Uncommon: Hypotension
Unknown: Orthostatic hypotension

Respiratory, thoracic and mediastinal disorders
Common: Dyspnea

Gastrointestinal disorders
Common: Abdominal pain, vomiting, nausea, diarrhea, constipation, dry mouth
Uncommon: Abdominal distension, flatulence
Unknown: Eructation, gastrointestinal discomfort

Hepatobiliary disorders
Common: Impaired liver function[6]
Unknown: Hepatocellular injury, cholestasis, hepatitis, jaundice

Skin and subcutaneous tissue disorders

Uncommon: Urticaria, pruritus, rash, erythema
Unknown: Acute generalized exanthematous pustulosis

Musculoskeletal and connective tissue and bone disorders
Unknown: Lupus-like syndrome

Reproductive system and breast disorders
Uncommon: Erectile dysfunction
Unknown: Decrease in sperm count[7]

General disorders and diseases related to the administration site
Common: Chest pain, weakness, fatigue, pyrexia

1. May present itself with cholestasis, blood dyscrasias, and rash.
2. Except vertigo.
3. Including sinoatrial block, atrioventricular block, and intraventricular block.
4. Propafenone may be associated with proarrhythmic effects manifesting as increased heart rate (tachycardia) or ventricular fibrillation. Some of these arrhythmias can be life-threatening and may require resuscitation to prevent potentially fatal outcomes.
5. Pre-existing heart failure may worsen.
6. This term includes abnormal liver function tests such as elevated aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, and blood alkaline phosphatase.
7. Decreased sperm count recovers after discontinuation of propafenone.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose and treatment
Symptoms:
Myocardial symptoms
The effects of propafenone hydrochloride overdose on the myocardium may include disturbances in impulse formation and conduction such as PQ interval prolongation, QRS complex widening, suppression of sinus node automaticity, AV block, ventricular tachycardia, ventricular flutter, ventricular fibrillation, and cardiac arrest. Reduced contractility (negative inotropic effect) may lead to hypotension that can result in cardiovascular shock in severe cases.

Non-cardiac findings and symptoms

In cases of overdose, metabolic acidosis, headache, dizziness, blurred vision, paresthesia, tremor, nausea, constipation, dry mouth, and convulsions have been reported. Fatal cases have also been reported.

In cases of severe poisoning, clonic-tonic convulsions, paresthesia, somnolence, coma, and respiratory arrest may occur.

Treatment:
In addition to general emergency measures, the patient's vital signs should be monitored and adjusted when necessary under intensive care conditions.

For control of rhythm and blood pressure, dopamine and isoproterenol infusions have been effective, as well as defibrillation. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory support and cardiac massage may be necessary.

Due to the high protein binding (95%) and large volume of distribution, hemodialysis is ineffective and attempts at elimination by hemoperfusion are of limited effect.

5. PHARMACOLOGICAL PROPERTIES

Propafenone hydrochloride is a class Ic antiarrhythmic drug that exhibits some structural similarities with beta-blocking agents.

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antiarrhythmics agents, class 1c
ATC code: C01BC03

Propafenone hydrochloride is an antiarrhythmic agent with membrane-stabilizing, sodium channel-blocking (Vaughan Williams, Class 1c) properties andlocal anesthetic activity. Its antiarrhythmic effects include slowing the rate of rise of the action potential, reducing excitability, homogenizing the conduction velocity, suppressing ectopic automatic impulses, and decreasing myocardial susceptibility to fibrillation. It also possesses weak beta-blocking activity (Vaughan Williams, Class II). However, at high doses (900–1200 mg), it may trigger sympatholytic (anti-adrenergic) effects. Propafenone hydrochloride slows impulse conduction (negative dromotropic effect) by reducing the rate of rise of the action potential. It prolongs the refractory periods in the atria, atrioventricular (AV) node, and ventricles. Thus, it exhibits a significant effect in treatment of heart rhythm disturbances of various origins. In patients with WPW syndrome, propafenone hydrochloride prolongs the refractory periods in accessory pathways.
On ECG, propafenone causes a slight prolongation of the P, PR, and QRS intervals, but as a rule the QTc interval is not affected.
In digitized patients with an ejection fraction of 35–50%, left ventricular contractility is slightly reduced. In patients with acute transmural infarction and heart failure, intravenous administration of propafenone significantly reduced left ventricular ejection fraction; but to a

lesser extent in patients in the acute stages of infarction without heart failure. In both scenarios, pulmonary arterial pressure showed only minimal increases. No significant changes in peripheral arterial pressure were observed. This suggests that propafenone did not cause an adverse effect on left ventricular function that could be considered clinically relevant. A clinically significant decrease in left ventricular function is only expected in patients with pre-existing impaired ventricular function.

5.2. Pharmacokinetic properties

Propafenone is a racemic mixture of S- and R-propafenone.

Absorption:

After oral administration, propafenone is almost completely absorbed from the gastrointestinal tract in a dose-dependent manner. Maximum plasma concentration is reached within 2–3 hours after administration of propafenone hydrochloride. The bioavailability after a single tablet dose is approximately 50%. With repeated dosing, plasma concentrations and bioavailability increase disproportionately due to saturation of the hepatic first-pass metabolism (CYP2D6). In single-dose studies, food was shown to increase the maximum plasma concentration and bioavailability, but in multiple-dose studies conducted in healthy individuals, food did not significantly alter the bioavailability of propafenone.

Distribution:

Propafenone is rapidly distributed throughout the body. The steady-state volume of distribution is1.9-3.0 L/kg. The therapeutic plasma levels are between 150-1500 ng/mL. Plasma protein binding of propafenone is concentration-dependent: at a concentration of 0.25 µg/mL, binding is 97.3%, and at 100 µg/mL, it decreases to 81.3%. Within the therapeutic concentration range, at least 95% of propafenone is bound to plasma proteins.

Biotransformation and elimination:

In a 24-hour cumulative urinary excretion comparison, it was found that 1.3% of an intravenous dose (70 mg) and 0.65% of an oral dose (600 mg) were excreted unchanged in the urine. Propafenone is almost completely metabolized in the liver. The estimated elimination half-life of propafenone is 2–10 hours in extensive metabolizers and 10–32 hours in poor metabolizers. A positive and close correlation has been found between plasma levels and AV conduction time in both healthy volunteers and most patients. The clearance of propafenone is 0.67–0.81 L/hour/kg.

After plasma levels of 500 ng/ml, the PR interval is statistically significantly prolonged compared to baseline measurements that allow dose titration and ECG monitoring of the patient. The frequency of ventricular extrasystoles decreases as plasma concentrations increase. In isolated cases, adequate antiarrhythmic activity has been observed at plasma concentrations below 500 ng/mL. Bioavailability approaches 100%, and steady state is achieved within 3 to 4 days. The recommended dosing regimen of propafenone is the same for all patients, regardless of metabolic status (extensive or poor metabolizers).

Linearity/Non-linearity:

No data available.

Geriatric population:
Exposure to propafenone in elderly patients with normal renal function is highly variable and does not differ significantly from that in younger healthy individuals. Exposure to 5-hydroxypropafenone was also found to be similar, but exposure to propafenone glucuronide was doubled.

Renal impairment
Even in the presence of renal dysfunction, reduced elimination of propafenone is not possible; this has been confirmed by case reports and kinetic studies in patients undergoing chronic hemodialysis. However, accumulation of glucuronide metabolites has been observed. Clinical chemistry parameters have not differed from those observed in individuals with normal renal function. Propafenone hydrochloride should be administered cautiously in patients with renal disease.

Hepatic impairment
In patients with hepatic impairment, both oral bioavailability and the elimination half-life of propafenone were increased. Dose adjustment is necessary in patients with liver disease.

5.3. Preclinical safety data
Preclinical data from studies based on conventional safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity do not indicate any special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Microcrystalline cellulose (Avicel PH-101)
Croscarmellose sodium
Maize starch
Hydroxypropyl methylcellulose
Microcrystalline cellulose (Avicel PH-102)
Magnesium stearate

Opadry® White 03G28692 (*film coating):*
Hydroxypropyl methylcellulose
Titanium dioxide
Polyethylene glycol-MW60000
Polyethylene glycol-MW400

6.2. Incompatibilities
No incompatibilities have been reported.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C.

6.5. Nature and contents of the container
Our product is used as a primary packaging material in blisters made of transparent PVC/PE/PVDC and aluminum foil. Blisters are packed in cartonboard boxes. Each carton contains 30 film-coated tablets in blister packs and is supplied with a package leaflet.

6.6. Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-posta: deva@devaholding.com.tr

8. MARKETING AUTHORIZATION NUMBER
2023/351

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorisation: 10.09.2023
Date of latest renewal: –

10. DATE OF REVISION OF THE SPC