Summary of Product Characteristics
(Product Data Sheet)

1. Name of the Medical Product

Product Name : **RIDMAL 40/320**

1.2 Strength : Dihydroartemisinin 40mg And Piperaquine Phosphate 320mg Tablets

1.3 Pharmaceutical Dosage Form : Oral Tablets

2. Qualitative & Quantitative Composition:

Ingredients	Theoretical quantity per tablet in mg
Dihydroartemisinin	40.000
Piperaquine Phosphate	320.000
Microcrystalline Cellulose	115.000
Povidone	5.000
Isopropyl Alcohol	q.s
Croscarmellose Sodium	10.000
Magnesium Stearate	10.000
Instacoat SOL IC-S-168	15.000
Methylene Chloride	q.s

3. Pharmaceutical Form:

Blue coloured, oval shaped, biconvex, film coated tablets.

4. Clinical Particulars

4.1 Therapeutic Indications:
Ridmal is indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, children and infants 6 months and over and weighing 5 kg or more.
Consideration should be given to official guidance on the appropriate use of antimalarial agents.

4.2 Posology and Method of administration:
Dosage
Patient should follow doctor's instruction. The recommended dosage is in the following table.

Body weight (kg)	Day 1	Day 2	Day 3	Total
	0 Hours	24 Hours	48 hours	
From 13 kg up to 24 kg	1 Tablet	1 Table	1 Table	3 Tablets
From 24 kg up to 36 kg	2 Tablets	2 Tablets	2 Table	6 Tablets
From 36 kg up to 75 kg	3 Tablets	3 Tablets	3 Table	9 Tablets
From 75 kg and above	4 Tablets	4 Tablets	4 Table	12 Tablets

Per dose = Per day (As recommended dosage is once daily)
No .Of Tablets per dose mentioned are to be taken together.

4.3 Contraindications:
Hypersensitivity to any of the components of the formulation.
As all new drugs. Ridmal is not recommended during the first trimester of pregnancy unless your doctor considers the risk of the disease to be greater.
A new course of Ridmal should not be taken within four weeks after the first treatment.

4.4 Special warning and precautions for use:
Ridmal should not be used to treat severe falciparum malaria and, due to insufficient data, should not be used to treat malaria due to Plasmodium vivax, Plasmodium malariae or Plasmodium ovale.
The long half-life of Piperaquine (about 22 days) should be kept in mind in the event that another anti- malarial agent is started due to treatment failure or a new malaria infection.
Piperaquine is an inhibitor of CYP3A4. Caution is recommended when co-administering Ridmal with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered.
Ridmal should not be used during pregnancy in situations where other suitable and effective antimalarials are available. In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Ridmal should be given in a 12- month period.
Pediatric Use:
Ridmal is indicated in children and infants 6 months and over and weighing 5 kg or more.

4.5 Interactions with other medicinal products and other forms of Interactions :
Ridmal is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval.
Drug-drug pharmacokinetic interaction studies with Ridmal have not been performed. The assessment of the potential for drug-drug interactions to occur is based on in vitro studies.
Effect of Ridmal on co-administered medicinal products
Piperaquine is metabolized by, and is an inhibitor of CYP3A4. Therefore, it has the potential to

increase plasma concentrations of other substrates for this enzyme (e.g. HMG CoA reductase inhibitors) with the risk of increased toxicity. Particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with Ridmal.

Piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity.

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

Dihydroartemisinin administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Ridmal is administered concomitantly with medicinal products metabolized by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of Dihydroartemisinin.

Effect of co-administered medicinal products on Ridmal

Piperaquine is metabolized by CYP3A4 in vitro. The contribution of CYP3A4 to elimination of Piperaquine in vivo is unknown. Concomitant treatment with medicinal products which inhibit CYP3A4 may lead to a marked increase of Piperaquine plasma concentration resulting in an exacerbation of the effect on QTc. Therefore, particular caution is required if Ridmal is administered to patients taking such medicinal products (e.g. some protease inhibitors [amprenavir, atazanavir, indinavir, nelfinavir, ritonavir], nefazodone or verapamil), and ECG monitoring should be considered due to the risk of higher plasma concentrations of Piperaquine.

All these potential interactions should be kept in mind for patients who require Ridmal treatment and, due to the long half-life of Piperaquine, for up to 3 months after the treatment.

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (Hypericum perforatum) are likely to lead to reduced Piperaquine plasma concentrations. The concentration of Dihydroartemisinin may also be reduced. Concomitant treatment with such medicinal products is not recommended.

Food interaction

Absorption of Piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Therefore, Ridmal should be taken with water. Ridmal should not be taken with grapefruit juice as it is likely to lead to increased Piperaquine plasma concentrations.

4.6 Pregnancy and Lactation:

Pregnancy

There are insufficient data on the use of DHA and piperaquine in pregnant women. Based on animal data, Ridmal is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation. Piperaquine was not teratogenic in the rat or rabbit. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal

	development following exposure in utero or via milk. Ridmal should not be used during pregnancy in situations where other suitable and effective anti- malarials are available. ***Nursing mothers*** Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Ridmal should not breast-feed during their treatment.
	4.7 Effects on ability to drive and use machine: The ability to drive and operate heavy machinery may be impaired during acute infection with malaria. Hence, patients on Ridmal must not attempt to drive or operate heavy machinery during acute infection.
	4.8 Undesirable Effects: Few cases of adverse effects have been reported after administration of combination of Dihydroartemisinin and Piperaquine. Most of them are related to Piperaquine affecting the digestive tract (nausea, diarrhea, loss of appetite, etc). Rare allergic reactions have also been reported - rash, pruritus etc.)
	4.9 Overdosage: In clinical trials, nine patients received double the cumulative intended dose of Ridmal. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: **Pharmacodynamic Properties:** **Pharmacotherapeutic Group: Antiprotozoals, Antimalarials,** **ATC Code: P01BF05** **Mechanism of Action:** Dihydroartemisinin is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including - Inhibition of falciparum sarcoplasmic-endoplasmic reticulum calcium ATPase, interference with mitochondrial electron transport, interference with parasite transport proteins and disruption of parasite mitochondrial function. The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step. Piperaquine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine- resistant Plasmodium strains in vitro. The bulky bisquinolone structure may be important for activity against chloroquine- resistant strains, and may act through the following mechanisms - Inhibition of the transporters that efflux chloroquine from the parasite food vacuole and inhibition of haem-digestion pathway in the parasite food vacuole. Resistance to piperaquine (when used as monotherapy) has been reported.
	5.2 Pharmacokinetics Properties: **Absorption** Dihydroartemisinin is very rapidly absorbed, Tmax being approximately 1-2 hrs after single

and multiple dosing. Dihydroartemisinin bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria has an effect on Dihydroartemisinin disposition. In healthy male volunteers under fasting conditions, mean Cmax and AUCINF of Dihydroartemisinin ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a Tmax of approximately 5 hours following a single and repeated dose. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. In healthy volunteers, piperaquine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Ridmal should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose.

Distribution
Both piperaquine and Dihydroartemisinin are highly bound to human plasma proteins: the protein binding observed in in vitro studies was 44-93 % for Dihydroartemisinin and >99 % for piperaquine. Moreover, from in vitro and in vivo data in animals, piperaquine and Dihydroartemisinin tend to accumulate in RBC.

Dihydroartemisinin was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5 %). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV % 37.5 %).

Biotransformation:
Dihydroartemisinin is principally converted to a-Dihydroartemisinin-ß-glucuronide (a-Dihydroartemisinin-G). In vitro drug-drug interaction studies revealed that Dihydroartemisinin is an inhibitor of CYP1A2; therefore, there is the potential for Dihydroartemisinin to increase plasma concentrations of CYP1A2 substrates.

The metabolism of piperaquine in humans has not been studied in vivo. In vitro metabolism studies demonstrated that piperaquine is metabolized by human hepatocytes (approximately 85 % of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolized by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine was found to be an inhibitor of CYP3A4 (also in a time-dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1. As a consequence, there is the potential for increasing plasma concentrations of CYP3A4 substrates, and also for the increase of piperaquine plasma concentrations when Ridmal is concomitantly administered with CYP3A4 substrates, and CYP3A4 inhibitors, respectively.
No effect on the metabolite profile of piperaquine in human hepatocytes was observed when piperaquine was co-incubated with Dihydroartemisinin. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.

Elimination
The elimination half-life of Dihydroartemisinin is approximately 1 hour. Dihydroartemisinin is

eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding Dihydroartemisinin excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperaquine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was 2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperaquine accumulates after multiple dosing.

Animal studies showed that radiolabelled piperaquine is excreted by the biliary route, while urinary excretion is negligible.

5.3 Preclinical Safety data:

General toxicity

Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts. The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible. Dihydroartemisinin and piperaquine were not genotoxic/clastogenic based on in vitro and in vivo testing.

Dihydroartemisinin causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure in utero or via milk.

No reproduction toxicity studies have been performed with the combination of Dihydroartemisinin and piperaquine.

Central nervous system (CNS) toxicity

There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different Dihydroartemisinin pro-drugs. In humans, the potential neurotoxicity of orally administered Dihydroartemisinin can be considered highly unlikely, given the rapid clearance of Dihydroartemisinin, and its short exposure (3 days of treatment for malaria patients).

There was no evidence of Dihydroartemisinin-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity:

Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC50 was 0.15 µmol for piperaquine and 7.7 µmol for Dihydroartemisinin. The association of

	Dihydroartemisinin and piperaquine does not produce hERG inhibition greater than that of the single compounds. **Phototoxicity:** There are no phototoxicity concerns with Dihydroartemisinin, as it does not absorb in the range of 290-700 nm. Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** **Carcinogenesis, mutagenesis** No carcinogenicity studies have been performed. **Impairment of Fertility** There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Moreover, data obtained in animal studies show that fertility is unaffected by Dihydroartemisinin in both females and males.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Microcrystalline Cellulose, Povidone, Isopropyl Alcohol, Croscarmellose Sodium, Magnesium Stearate, Instacoat SOL IC-S-168 & Methylene Chloride
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 24 months from the date of manufacturer
	6.4 Special Precautions for storage: Store at a temperature below 30^0C. Protect from light and moisture.
	6.5 Nature and contents of container: 1. Alu – PVC/PVdC blister pack (1x3's) 3 tablets in a blister pack, 1 blister in a printed carton along with a pack insert. 2. Alu – PVC/PVdC blister pack (1x6's) 6 tablets in a blister pack, 1 blister in a printed carton along with a pack insert. 3. Alu – PVC/PVdC blister pack (1x9's) 9 tablets in a blister pack, 1 blister in a printed carton along with a pack insert. 4. Alu – PVC/PVdC blister pack (1x12's) 12 tablets in a blister pack, 1 blister in a printed carton along with a pack insert
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House,

	Charkop, Kandivli (West), Mumbai- 400 067, India
	Marketing Authorization Numbers: Not applicable
8.	**Date of first authorization/ renewal of the authorization:** Not applicable
9.	**Date of revision of text:** May 31, 2017