Summary of Product Characterstics

Timequin® Capsule

Timequin® Sachet

Timequin®

(Dihydroartemisinin + Piperaquine Phosphate)

1. NAME OF THE PRODUCT

Timequin® (Dihydroartemisinin + Piperaquine Phosphate) Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Timequin® Capsules

Each capsule contains:

Dihydroartemisinin Ph. Int.……..……40mg

Piperaquine Phosphate MS.....……320mg

3. PHARMACEUTICAL FORM

Capsule

Appearance: Yellow to dark yellow powder in hard gelatin capsules having dark purple opaque cap printed "**Timequin®**" and blue opaque body with "" printed on it 3 times.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

World Health Organization (WHO) strongly recommends **Timequin®** as a latest ACT option to use as first line treatment for the uncomplicated *P. falciparum* malaria including multi-drug-resistant strains. **Timequin®** is also effective against *P. vivax* malaria and has strong action on gametocytes. Piperaquine is also used as prophylaxis due to the advantage of its longer half-life.

Timequin® capsules are indicated for all kinds of malaria, especially malaria caused by multi resistant *Plasmodium falciparum*.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Oral dosage of **Timequin®** capsules as per following schedule in different age groups are given below:

Age (Years)	7-10 years	11-15 years	≥16 years
Initial	1 capsule	2 capsules	2 capsules
6th hrs	1 capsule	1 capsule	2 capsules
24th hrs	1 capsule	1 capsule	2 capsules
32nd hrs	1 capsule	2 capsules	2 capsules

Elderly: Considering the possibility of age associated decrease in hepatic and renal function, as well as a potential for heart disorders, caution should be exercised when administering the product to the elderly.

Method of administration:
Timequin® capsules should be taken orally with water and without food.
Each dose should be taken no less than 3 hours after the last food intake.
No food should be taken within 3 hours after each dose.

4.3. CONTRAINDICATIONS:

- Patients with hypersensitivity to any of Artemisinin's derivative and piperaquine phosphate component.
- Severe malaria according to WHO definition.
- Family history of sudden death or of congenital prolongation of the QTc interval.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia. Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
  - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
  - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
  - Certain antimicrobial agents, including agents of the following classes:
    - macrolides (e.g. erythromycin, clarithromycin),
    - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
    - imidazole and triazole antifungal agents,
    - and also pentamidine and saquinavir
- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Dihydroartemisinin + Piperaquine

Phosphate is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate 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.
Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate should be given in a 12- month period.

Effects on cardiac repolarization:

QTc prolongation occurred more frequently and to a larger extent in association with Dihydroartemisinin + Piperaquine Phosphate therapy than with the comparators. Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Dihydroartemisinin + Piperaquine Phosphate treated patients than in those treated with comparator antimalarial.
An ECG should be obtained as early as possible during treatment with Dihydroartemisinin + Piperaquine Phosphate and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation.
When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period. QTc intervals of more than 500 ms are associated with a pronounced risk for potentially life- threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24-48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive another dose of Dihydroartemisinin + Piperaquine Phosphate and alternative antimalarial therapy should be instituted.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Dihydroartemisinin + Piperaquine Phosphate so that special caution is required.

Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Dihydroartemisinin + Piperaquine Phosphate.

Piperaquine is metabolized by and is an inhibitor of CYP3A4. There is a potential for a several-fold increase of piperaquine plasma concentrations when it is co-administered with other CYP3A4 substrates (due to competition) and, especially, with CYP3A4 inhibitors, resulting in an exacerbation of the effect on QTc prolongation. Therefore, particular caution is required if Dihydroartemisinin + Piperaquine Phosphate is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine.

Dihydroartemisinin + Piperaquine Phosphate has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Dihydroartemisinin + Piperaquine Phosphate is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Dihydroartemisinin + Piperaquine Phosphate 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.

Effect of 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 ciclosporin) are co-administered with Dihydroartemisinin + Piperaquine Phosphate.

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.
DHA administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Dihydroartemisinin + Piperaquine Phosphate 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 DHA.
Effect of co-administered medicinal products on Dihydroartemisinin + Piperaquine Phosphate:
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 Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate 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 DHA 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, Dihydroartemisinin + Piperaquine Phosphate should be taken with water. Dihydroartemisinin + Piperaquine Phosphate should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6. FERTILITY, PREGNANCY AND LACTATION:

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 DHA in both females and males.
Pregnancy: There are insufficient data on the use of DHA and piperaquine in pregnant women. Dihydroartemisinin + Piperaquine Phosphate 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 is associated with delivery complications. However,

there is no delay in neonatal development following exposure in utero or via milk. Dihydroartemisinin + Piperaquine Phosphate should not be used during pregnancy in situations where other suitable and effective anti-malarials are available.

Breast-feeding: Women taking Dihydroartemisinin + Piperaquine Phosphate should not breast-feed during their treatment. No data is seen whether traces are found in mother's milk. In case of doubt, seek the advice of the physician. In order to avoid any possible drug interaction, kindly inform the physician.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Dihydroartemisinin + Piperaquine Phosphate has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.8. UNDESIRABLE EFFECTS:

In several patients treated with Dihydroartemisinin + Piperaquine Phosphate, no severe adverse effects have been reported.

Adverse effects seen are usually light and disappear when the treatment is stopped. The common side effects are nausea, vomiting, stomachache, diarrhoea, headache, dizziness itching pruritus etc.

Nausea and vomiting occurs occasionally with incidence of less than 6%. No side effects have been reported for Dihydroartemisinin. Dihydroartemisinin can cause a reversible reduction in reticulocyte count in certain individuals. Possible side effects of Piperaquine Phosphate include mild nausea, vomiting and abdominal discomfort. Occasional leucopenia was seen in some cases with dyspnoea and palpitations but not specified.

The adverse reactions ranked under headings of system organ class and frequency using the following convention: 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) for VTEp, NVAF, and VTEt respectively.

Infections and infestations:

Common: *P. falciparum* infection

Uncommon: Influenza Respiratory tract infection

Blood and lymphatic system disorders:

Common: Anaemia

Metabolism and nutrition disorders:

Uncommon: Anorexia

Nervous system disorders:

Common: Headache

Uncommon: Dizziness, convulsion

Cardiac disorders:

Common: QTc prolonged, tachycardia

Uncommon: Cardiac conduction disorders, sinus arrhythmias, bradycardia
Respiratory, thoracic and mediastinal disorders:
Uncommon: Cough
Gastrointestinal disorders:
Uncommon: Vomiting, abdominal pain, diarrhoea, nausea
Hepatobiliary disorders:
Uncommon: Hepatitis, hepatomegaly, abnormal liver function tests
Skin and subcutaneous Tissue disorders:
Uncommon: Pruritis
Musculoskeletal and connective tissue disorders:
Uncommon: Arthralgia, myalgia
General disorders and administration site conditions:
Common: Asthenia, pyrexia

4.9. OVERDOSE:

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation.
In cases of suspected overdose, symptomatic therapy should be given without any delay.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antiprotozoals, Antimalarials
ATC Code: P01BF05
Mechanism of action: Dihydroartemisinin has fastest action on malarial parasite among all artemisinin derivatives by rapidly eliminating blood schizonts and also have strong effect on early and late trophozoites. Dihydroartemisinin concentrates selectively into cells contracted by parasites and reacts with heam to kill the parasites. This reaction produces poisonous free radicals that can destroy membranes of parasites. Piperaquine, a derivative of 4-aminoquino-line group, have strong action on blood schizonts and late trophozoites. Piperaquine inhibits the heamozoin formation and interacts with the heam to ferriprotoporphyrin-piperaquine complex (FP-Piperaquine complex) which is highly toxic and damage the membrane of all types of malarial parasites and destroy them effectively. Both Dihydroartemisinin and Piperaquine also have strong action on gametocytes which help to prevent the. malaria transmission.

5.2. PHARMACOKINETICS PROPERTIES:

Dihydroartemisinin is rapidly absorbed on oral administration and peak plasma concentration is attained 1 hour afterwards, with a half-life of about 4 hours. It is widely distributed in body with more concentration in the liver, kidneys and bile. 80% excretion is through the urine and faeces within 24 hours after

administration. Piperaquine Phosphate (80-90%) is absorbed within 24 hours. It is widely distributed in the body mainly in the liver, kidneys, lungs and spleen. 25% of total dose is accumulated in the liver within 8 hours of intact. Elimination is very slow with the half-life of about 9.4 days. It is excreted through bile by hepatoenteral circulation.

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. DHA and piperaquine were not genotoxic/clastogenic based on in vitro and in vivo testing. No carcinogenicity studies have been performed. DHA 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 DHA 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 DHA pro-drugs. In humans, the potential neurotoxicity of orally administered DHA can be considered highly unlikely, given the rapid clearance of DHA, and its short exposure (3 days of treatment for malaria patients). There was no evidence of DHA-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 DHA. The association of DHA and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity: There are no phototoxicity concerns with DHA, 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Lactose Monohydrate
- Microcrystalline Cellulose
- Crosscarmellose Sodium
- Sodium Stearyl Fumarate
- Hard Gelatin Capsule

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.
Avoid exposure to heat light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/PVC blister packing, pack size is 8's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

SAMI's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

070786

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

18th August, 2011

10. DATE OF REVISION OF THE TEXT

ٹائم کوئین® کیپسول

(ڈائی ہائیڈروآرٹیمیسنن + پیپراکوئین فاسفیٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

Timequin®

(Dihydroartemisinin + Piperaquine Phosphate)

1. NAME OF THE PRODUCT

Timequin® (Dihydroartemisinin + Piperaquine Phosphate) 15/120 Sachets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Timequin® 15/120 Sachets

Each sachet contains:

Dihydroartemisinin Ph. Int.……15mg

Piperaquine Phosphate MS……120mg

3. PHARMACEUTICAL FORM

Granular Powder for Oral Suspension

Appearance: Light orange coloured granular powder having characteristic odor.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

World Health Organization (WHO) strongly recommends **Timequin®** (Dihydroartemisinin + Piperaquine Phosphate) as a latest ACT option to use as first line treatment for the uncomplicated *P. falciparum* malaria including multi-drug-resistant strains. **Timequin®** is also effective against *P. vivax* malaria and has strong action on gametocytes. Piperaquine is also used as prophylaxis due to the advantage of its longer half-life.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Timequin® is administered as once daily for 3 days course for the treatment of Malaria. The recommended dose of Dihydroartemisinin is given 4mg/kg/day & Piperaquine Phosphate is given 32mg/kg/day.

Sachet Dose:

Body weight	Day 1	Day 2	Day 3
5 to <7kg	1 sachet	1 sachet	1 sachet
7 to <13kg	2 sachets	2 sachets	2 sachets
13 to <25kg	3-3.5 sachets	3-3.5 sachets	3-3.5 sachets

Method of administration:

Pour the granules of sachet into some water and drink.

To achieve high clinical cure rate, the drug should be taken at 0, 6, 24 hours and 48 hours.

4.3. CONTRAINDICATIONS:

- Patients with hypersensitivity to any of Artemisinin's derivative and piperaquine phosphate component.
- Severe malaria according to WHO definition.
- Family history of sudden death or of congenital prolongation of the QTc interval.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia. Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
  - Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
  - Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
  - Certain antimicrobial agents, including agents of the following classes:
    - macrolides (e.g. erythromycin, clarithromycin),
    - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
    - imidazole and triazole antifungal agents,
    - and also pentamidine and saquinavir
- Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
- Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that **Timequin®** is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate 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.

Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate should be given in a 12- month period.

Effects on cardiac repolarization:

QTc prolongation occurred more frequently and to a larger extent in association with Dihydroartemisinin + Piperaquine Phosphate therapy than with the comparators. Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Dihydroartemisinin + Piperaquine Phosphate treated patients than in those treated with comparator antimalarial.

An ECG should be obtained as early as possible during treatment with Dihydroartemisinin + Piperaquine Phosphate and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation.

When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period. QTc intervals of more than 500ms are associated with a pronounced risk for potentially life threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24-48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive another dose of Dihydroartemisinin + Piperaquine Phosphate and alternative antimalarial therapy should be instituted.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Dihydroartemisinin + Piperaquine Phosphate so that special caution is required.

Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Dihydroartemisinin + Piperaquine Phosphate.

Piperaquine is metabolized by and is an inhibitor of CYP3A4. There is a potential for a several-fold increase of piperaquine plasma concentrations when it is co-administered with other CYP3A4 substrates (due to competition) and, especially, with CYP3A4 inhibitors, resulting in an exacerbation of the effect on

QTc prolongation. Therefore, particular caution is required if Dihydroartemisinin + Piperaquine Phosphate is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine.

Dihydroartemisinin + Piperaquine Phosphate has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Dihydroartemisinin + Piperaquine Phosphate is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Dihydroartemisinin + Piperaquine Phosphate 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.

Effect of 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 ciclosporin) are co-administered with Dihydroartemisinin + Piperaquine Phosphate.

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 Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate:

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 Dihydroartemisinin + Piperaquine Phosphate 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 Dihydroartemisinin + Piperaquine Phosphate 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, Dihydroartemisinin + Piperaquine Phosphate should be taken with water. Dihydroartemisinin + Piperaquine Phosphate should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6. FERTILITY, PREGNANCY AND LACTATION:

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.

Pregnancy: There are insufficient data on the use of Dihydroartemisinin and piperaquine in pregnant women. Dihydroartemisinin + Piperaquine Phosphate 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 is associated with delivery complications. However, there is no delay in neonatal development following exposure *in utero* or via milk. Dihydroartemisinin + Piperaquine Phosphate should not be used during pregnancy in situations where other suitable and effective anti-malarials are available.

Breast-feeding: Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Dihydroartemisinin + Piperaquine Phosphate should not breast-feed during their treatment.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Adverse event data collected in clinical trials suggest that Dihydroartemisinin + Piperaquine Phosphate has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.8. UNDESIRABLE EFFECTS:

The adverse reactions ranked under headings of system organ class and frequency using the following convention: 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: *P. falciparum* infection
Uncommon: Influenza, respiratory tract infection
Blood and lymphatic system disorders:
Common: Anaemia
Metabolism and nutrition disorders:
Uncommon: Anorexia
Nervous system disorders:
Common: Headache
Uncommon: Dizziness, convulsion
Cardiac disorders:
Common: QTc prolonged, tachycardia
Uncommon: Cardiac conduction disorders, sinus arrhythmias, bradycardia
Respiratory, thoracic and mediastinal disorders:
Uncommon: Cough
Gastrointestinal disorders:
Uncommon: Vomiting, abdominal pain, diarrhoea, nausea
Hepatobiliary disorders:
Uncommon: Hepatitis, hepatomegaly, abnormal liver function tests
Skin and subcutaneous tissue disorders:
Uncommon: Pruritis
Musculoskeletal and connective tissue disorders:
Uncommon: Arthralgia, myalgia
General disorders and administration site conditions:
Common: Asthenia, pyrexia

4.9. OVERDOSE:

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antiprotozoals, Antimalarials

ATC Code: P01BF05

Mechanism of action: Dihydroartemisinin has fastest action on malarial parasite among all artemisinin derivatives by rapidly eliminating blood schizonts and also have strong effect on early and late trophozoites. Dihydroartemisinin concentrates selectively into cells contracted by parasites and reacts with heam to kill the parasites. This reaction produces poisonous free radicals that can destroy membranes of parasites. Piperaquine, a derivative of 4-aminoquino-line group, have strong action on blood schizonts and late trophozoites. Piperaquine inhibits the heamozoin formation and interacts with the heam to ferriprotoporphyrin-piperaquine complex (FP-Piperaquine complex) which is highly toxic and damage the membrane of all types of malarial parasites and destroy them effectively. Both Dihydroartemisinin and Piperaquine also have strong action on gametocytes which help to prevent the. malaria transmission.

5.2. PHARMACOKINETICS PROPERTIES:

Oral Dihydroartemisinin is rapidly & completely absorbed within 1 hrs and achieves peak plasma level within 0.6 hrs after absorption with C_{max} of 360 (181-658)ng/ml, AUC24 907 (324-2,289)ng/ml. Elimination half-life of Dihydroartemisinin is 3.1 hrs after oral administration.

Piperaquine is rapidly absorbed and achieves peak plasma level within 4-7 hrs after oral administration. C_{max} achieves 232ng/ml within (T_{max}) 3hrs. AUC_{24} of Piperaquine is 13441ng/ml and elimination half-life of Piperaquine is 20-25 days. There is minimal effect of food on the absorption of Piperaquine thus no specific food instructions are required at the time of Piperaquine administration.

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. No carcinogenicity studies have been performed. 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 80mg/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 IC_{50} was 0.15µmol for piperaquine and 7.7µmol 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 290-700nm. Piperaquine has an absorption maximum at 352nm. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Indion
- Mannitol
- Sucrose
- Methyl Paraben
- Propyl Paraben
- Titanium Dioxide
- Simethicone LVA
- Sucralose
- Neotame Powder
- Trusil Orange Powder Flavor
- Sunset Yellow Lake Color
- Purified Water

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.
Avoid exposure to heat light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

6.5. NATURE AND CONTENTS OF CONTAINER:

Paper foil sachet, pack size is 16's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

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

6.7. DRUG PRODUCT SPECIFICATIONS:

SAMI's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

070787

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

18th August, 2011

10. DATE OF REVISION OF THE TEXT

ٹائم کوئین® ساشے

(ڈائی ہائیڈرو آرٹیمیسنن + پیپر اکوئین فاسفیٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔