1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Please see the following page.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DUO-COTECXIN Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DUO-COTECXIN: Each tablet contains 40mg of Dihydroartemisinin and 320mg of Piperaquine phosphate.

Piperaquine phosphate is present as anhydrous basis.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORMULATION

DUO-COTECXIN tablet is a round biconvex blue film coated tablet with 'D.C' debossed on one side and a score line on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

One box contains 9 tablets in thick PVC + Aluminum foil blister cards

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic indications

This medicine is an antimalarial medicine. It contains DIHYDROARTEMISININ and PIPERAQUINE. It is indicated in the treatment of un-complicated *falciparum* malaria, particularly in case of resistance to other antimalarials. Recent studies demonstrated that it was also efficient in *vivax* malaria

4.2 Posology and method of administration

HOW TO TAKE DUO-COTECXIN

Always take DUO-COTECXIN* exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

When taking DUO-COTECXIN

- ✓ Swallow the tablets with a ittle water, after a meal,
- ✓ For young children, tablets can be crushed and given with some water.
- ✓ Medicines are given only once a day. A complete treatment course is 3 days.

Recommended dosage regimen by WHO

BodyWeight(kg)	Dihydroartemisinin/Piperaquine(mg)		
	1st day	2nd day	3rd day
5to<8	20mg/160mg	20mg/160mg	20mg/160mg
8to<11	30mg/240mg	30mg/240mg	30mg/240mg
11to<17	40mg/320mg	40mg/320mg	40mg/320mg
17to<25	60mg/480mg	60mg/480mg	60mg/480mg
25to<36	80mg/640mg	80mg/640mg	80mg/640mg
36to<60	120mg/960mg	120mg/960mg	120mg/960mg
60to<80	160mg/1280mg	160mg/1280mg	160mg/1280mg
>80	200mg/1600mg	200mg/1600mg	200mg/1600mg

If you take more Duo-Cotecxin than you should have, please consult your doctor or pharmacist.

How long should you take DUO-COTECXIN*

Do not stop your treatment before the recommended time (3 days), even if your symptoms have disappeared; you may have a relapse.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4.3 Contraindications

- Linked to PIPERAQUINE

See section 4.6 Pregnancy and breast feeding

- Linked to DIHYDROARTEMISININE

See section 4.6 Pregnancy and breast feeding

4.4 Special warnings and precaution for use

- PIPERAQUINE

Do not exceed the prescribed dose

- DIHYDROARTEMISININE

Do not exceed the prescribed dose

4.5 Interaction with other medicinal products and other forms of interaction

No information.

4.6 Pregnancy and lactation

- Pregnancy

Clinical data on PIPERAQUINE and DIHYDROARTEMISININ are not sufficient to assess their safety during pregnancy. In the absence of complete data, DUO-COTECXIN should not be used during pregnancy without medical supervision, especially during the first 3 months.

- Lactation

In the absence of data regarding the excretion into breast milk of PIPERAQUINE and DIHYDROARTEMISININ, the use of this medicine is to be avoided by nursing mothers.

4.7 Effect on ability to drive and use of machines

No information.

4.8 Undesirable effects

- Linked to PIPERAQUINE
  - Rare intestinal tract disorders: nausea, diarrhoea, anorexia
  - Rare allergic reactions: pruritus, cutaneous rash

- Linked to DIHYDROARTEMISININ

In some cases, changes in laboratory tests may occur: decrease of reticulocytes and slight increase of liver enzymes. Usually, no clinical disorders are associated to these changes.

4.9 Overdose

- PIPERAQUINE
  - Dangerous dose: in the absence of reported case, it cannot be evaluated precisely; by analogy to quinine derivatives, a special cardiac surveillance will be put into place.
  - Treatment: immediate transfer to a specialised unit.

- DIHYDROARTEMISININ

In case of overdose, a symptomatic treatment should be immediately started in a specialised unit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

- Linked to PIPERAQUINE

Antimalarial (P: parasitology)

PIPERAQUINE is a synthetic bisquinolein antimalarial which belongs to the 4-amino-quinolein group. It acts on the schizonts of *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malaria*. It treats acute malaria by combination to haemoglobin and production of a toxic compound destroying both parasites and red cells. After oral intake, the schizonticide efficacy has been demonstrated *in vivo* on strains of *P. berghei*.

There are numerous strains of *Plasmodium falciparum* which resist to 4-amino-quinolein drugs; their geographical distribution is in constant evolution. No documented resistance to piperaquine has been reported so far.

- Linked to DIHYDROARTEMISININ

Antimalarial (P: parasitology)

Dihydroartemisinin is synthesised by reduction of artemisinin. It acts by producing free radicals to inhibit *Plasmodium* protein synthesis, in particular the replication of nucleic acids and destroy both sexual and asexual elements including gametocytes, trophozoites and schizonts.

Its schizonticide efficacy, after oral intake, has been demonstrated *in vivo* on chloroquino-susceptible strains of *Plasmodium* (*P.berghei* in mice and *P.knowlesi* in monkeys) and on chloroquino-resistant strains (*P.berghei* in mice). In all animal models, the rapidity of action of oral dihydroartemisinin was always superior to chloroquinine (*per os*) and to quinine (IV) on all strains. In macaques (the animal model closest to man), the efficacy of DUO-COTECXIN was the same as quinine used at their usual doses.

No documented resistance to dihydroartemisinin has been reported so far.

5.2 Pharmacokinetics

- PIPERAQUINE

The estimated mean absorption half-life of piperaquine phosphate was about 9 days. 80-90% are absorbed in the gastrointestinal system and accumulated in liver, kidney; lung and spleen. 1/4 of the drug accumulates in the liver within 8hrs. C_{max} was usually observed between 7 and 12 hrs following drug administration. Piperaquine phosphate is highly protein bound (99.9%), the majority being bound to high density lipoproteins. Faeces and bile is the main excretion way. Only around 23% are excreted in 3 days after oral administration. The metabolism route of piperaquine phosphate is hepatoenteral.

- DIHYDROARTEMISININE

Dihydroartemisinin is rapidly absorbed, and is detected in the blood after 30 minutes. Peak plasma concentrations (C_{max}) of both compounds are achieved around 1.33 hours after drug administration. C_{max}= 0.71µg/ml, $T_{1/2}$=1.57h. DHA is almost totally metabolized with practically no parent compound being detected in the faeces or urine. DHA is highly protein bound to plasma proteins (>95%) with a large proportion (33%) being bound to α_1 glycoproteins. A variety of reduced metabolites are found in the urine. The radioactivity

decreased with the reduction of serum drug concentration accordingly. The biliary excretion of radioactivity also reached its peak in 1 hour. 82.7% of the total drug was excreted by urine and faeces, mainly in the urine which amounts to 67.1%.

5.3 Preclinical safety data

Pre-clinical studies of DUO-COTECXIN demonstrated its high efficacy, its good parasitic strains curative effect and quick onset of action. Both *in vitro* and *in vivo* test of DUO-COTECXIN on human malaria indicated that the two components had a synergistic efficacy. Toxicity studies, including chronic and acute toxicity in several animal species confirmed the perfect safety of DUO-COTECXIN, in particular on central nervous system and cardiac system. It also demonstrated the distribution of the product, mainly in the organs rich in haematopoietic tissues, such as liver and spleen.

6. PHARMACEUTICAL DATA

6.1List of excipients

Each tablet contains maize starch, dextrin, hypromellose, sodium starch glycolate and magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precaution for storage

To be stored in a place protected from light and humidity at a temperature inferior to 30°C

6.5 Nature and content for container

Each box contains a PVC/aluminium blister containing 8 tablets of a fixed combination of DIHYDROARTEMISININ and PIPERAQUINE and a Patient Information leaflet.

6.6 Special precautions for disposal

To be eliminated according to the local laws

7. MARKETING AUTHORISATION HOLDER(S)

Beijing Holley-Cotec Pharmaceutical Co., Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

GUOYAOZHUNZI H20059812

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2008-11-24

10. DATE OF REVISION OF THE TEXT

August, 2020