EXPERT REVIEW No. 1

Expert peer review on application for Colchicine (FMF)

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes No √ (if no, please provide reference and information)
      See attachment part 1-2.
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences).

      Colchicine was effective in preventing Familial Mediterranean Fever (FMF) attacks compared with placebo by four RCTs. It could prevent amyloidosis caused by FMF as well.

   c. Please provide any additional relevant information with reference
      See attachment part 1-2.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes No √ (if no, please provide reference and information)
      See attachment part 1-2.
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Colchicine causes ADRs in digestive system (Frequent: diarrhoea, nausea, vomiting. Rare: increase in transaminases), motor system (Infrequent: neuromyopathic disorders. Very rare: rhabdomyolysis), urogenital system (Exceptional: azoospermia. SAE: sperm chromosomal abnormalities, birth defects, miscarriage, infertility.) and some others (Infrequent: leucopenia, neutropenia, thrombopoenia. Rare: Urticaria, morbilliform eruptions.). If colchicine is taken over dose, it may cause toxicosis and even death.

   c. Please provide any additional relevant information with reference
      See attachment part 1-2.

3. Assessment of cost and availability
   a. Have all relevant data on cost provided
      Yes No √ (if no, please provide reference and information)
      See attachment part 1-2.
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      In China, colchicine tablet (0.5mg) × 30=¥10.50=$1.68. Therefore colchicine tablet 1mg costs 0.11 USD in China. Yucel et al reported the mean annual drug costs for FMF was about 82.43±20.93 USD.

   c. Please provide any additional relevant information with reference
      None

   d. Is the product available in several low and middle income countries?
Colchicine was included by National Essential Medicines List (2009 edition) and National Essential Medical Insurance Medicine List of China (2009 edition, 100% reimbursed) for the treatment of gout, since there was no FMF patient in China.

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences)

   FMF mainly affects populations surrounding the Mediterranean basin, especially Jews, Armenians, Arabs, and Turks. No study reported Chinese people suffering from FMF.

   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

      No guideline was found.

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

   Yes. It is appropriate to start colchicine from low dose(<5years: ≤0.5mg/day, 5~10years:1mg/day, >10years: 1.5mg/day) and adjust dosage by 0.25mg/step up to a maximum of 2mg/day.

   Renal and liver function should be monitored carefully.

6. Is the proposed product registered by a stringent regulatory authority?

   Yes √

7. Any other comments

   Yes √

8. What is your recommendation to the committee (please provide the rationale)

   We recommend colchicine be listed in WHO EML for FMF, due to:

   • Colchicine was effective in preventing FMF attacks as well as amyloidosis caused by FMF.
   • ADRs caused by colchicine are acceptable.
   • The cost of colchicine is low (approximately 0.11~0.13 USD per 1mg).
Peer Review Attachment

Comparison of Application and Evaluation for Colchicine (FMF)

### 1. Included Studies

<table>
<thead>
<tr>
<th>Items</th>
<th>Data of Application</th>
<th>Data of Evaluation</th>
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<tbody>
<tr>
<td></td>
<td>No. of IS</td>
<td>No. of IP</td>
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<tr>
<td>Economical Evaluation</td>
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### 2. Outcomes of Evaluation

**Efficacy**
- Prophylaxis of Attacks: Colchicine > PLB: P<0.05 (3RCTs)
- Prophylaxis of Amyloidosis: Colchicine vs no treatment: 0.4% vs 30%
- Treatment of Amyloidosis: Stabilizing or improving proteinuria secondary to amyloidosis: 66.36%(73/110)

**Safety**
- Digestive system: √ Frequent: diarrhoea, nausea, vomiting. Rare: increase in transaminases.
- Circulatory system: -
- Urogenital system: √ Exceptional: azoospermia.
- Nervous system: -
- Respiratory system: -
- Reproductive system: -
- Endocrine system: -
- Others: √ Infrequent: leucopenia, neutropenia, thrombopenia. Rare: Urticaria, morbilliform eruptions.

**Applicability**
- Prevent FMF attacks, Prevent and treat Amyloidosis.

Two more CCTs and one case series study indicate Colchicine is effective.

Colchicine > PLB: P<0.05 (1RCT)

Colchicine > PLB: P<0.05 (4RCTs)

66.36% + Two more CCTs + one case series study.

Idem + Diarrhoea 14.38%(22/153), Transaminases increased 11.76%(18/153)

√ Idem + Sperm chromosomal abnormalities* (1 case), Birth defects* (7 cases), Miscarriage* (7 cases), Infertility (13 cases).

√ Idem + Toxicosis* (4 cases due to over dose, 1 died, 1 toxic epidermal necrolysis-like exanthem).

Prevent FMF attacks, Prevent Amyloidosis.
### Economical Evaluation

0.11~0.13 USD for 1mg tablet.

In China, 0.11 USD for 1 mg tablet. Mean annual drug costs 82.43±20.93 USD from Yucel 2012.

<table>
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<tr>
<th>3. Quality of Evidence</th>
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<tr>
<td>4. Recommendation</td>
<td>For FMF and Amyloidosis caused by FMF.</td>
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</table>

Abbreviation: SR: systematic review, RCT: randomized controlled trial, CCT: controlled clinical trial, IS: included studies, IP: included patients, PLB: placebo, FMF: Familial Mediterranean Fever, √: reported, *: serious adverse reaction, -: no reports found. Frequent (≥ 1/100 and < 1/10), Infrequent (≥ 1/1000 and < 1/100), Rare (≥ 1/10000 and < 1/1000) and Very rare (< 1/10000)