The degree to which the phenylalanine levels are reduced in tetrahydrobiopterin deficiency patients upon administration of sapropterin dihydrochloride is not related to the unmet need in tetrahydrobiopterin deficiency. For patients with the same dose of L-DOPA, the child may benefit from the decreased phenylalanine levels of breast milk and additional sapropterin available from its mother (Kapatos et al. 1989).

### 4.10 Effects on ability to drive and use machines

L-dopa-responsive PKU patients are not at an increased risk of side effects while being treated with sapropterin dihydrochloride.

### 4.11 Undesirable effects

**Withdrawal effects**

Withdrawal effects may be seen in patients who are initiated on sapropterin dihydrochloride (Kapatos et al. 1991). Patients may experience a rebound increase of plasma phenylalanine levels during the 24 hours after the last dose of sapropterin dihydrochloride, followed by a decrease of the baseline phenylalanine levels in the following 24 hours.

**Other effects**

Other effects include sleep disorders, nightmares, insomnia, sleeplessness, irritability, anxiety, somnolence, depression, weight gain, myopathy, and paresthesia.

**Oscillations in plasma phenylalanine levels**

Oscillations in plasma phenylalanine levels may occur if the sapropterin dihydrochloride dose is increased during the loading phase. If the dose is increased, the patient should be monitored closely for a possible rebound increase in plasma phenylalanine levels during the 24 hours following the last dose of sapropterin dihydrochloride.

**Intracranial hypertension**

Some patients with PKU have undergone surgery for intracranial hypertension (Kapatos et al. 1989).

**Kidney function**

Kidney function can be impaired in patients with PKU, and the dose of sapropterin dihydrochloride should be reduced in patients with impaired renal function.

**Cardiovascular effects**

Cardiovascular effects can occur with the use of sapropterin dihydrochloride.

**Gastrointestinal effects**

Gastrointestinal effects can occur with the use of sapropterin dihydrochloride.

**Neurological effects**

Neurological effects can occur with the use of sapropterin dihydrochloride.

**Hepatic effects**

Hepatic effects can occur with the use of sapropterin dihydrochloride.

**Renal effects**

Renal effects can occur with the use of sapropterin dihydrochloride.

**Skin effects**

Skin effects can occur with the use of sapropterin dihydrochloride.

**Musculoskeletal effects**

Musculoskeletal effects can occur with the use of sapropterin dihydrochloride.

**Respiratory effects**

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4. PHARMACEUTICAL PARTICULARS

Please see the Teriobiopterin Tablets 100mg Label, which provides detailed information on tetrahydrobiopterin deficiencies and BH4 requirements prior to and during treatment.

5. List of excipients

Ascorbic acid
Acacia and Magnesium cellulose
Microcrystalline cellulose
Collagen

5.2 Preparation

Microcrystalline cellulose
Ascorbic acid

5.3 Preclinical safety data

Deficiency becomes apparent,
Sapropterin is rapidly absorbed mainly in the duodenum and the jejunum and less in the stomach. Absorption is more rapid
It was found that most of the ingested sapropterin dihydrochloride is absorbed in the gastrointestinal tract
In, a fully oxidized form of tetrahydrobiopterin, was not accumulated in any tissues and was excreted rapidly in the urine
The AUC 0-∞ ranged from 2959 to 3159 nmol·h/l for 10 mg/kg and was similar to 3603 nmol·h/l found for 20 mg/kg
Most of the ingested sapropterin dihydrochloride is absorbed in the gastrointestinal tract
in serum is about 3.5 hours (range 3.3-5.1)

6.6 Manufacturer

Al Aqeel, A., P. T. Ozand, et al. (1991). "Biopterin-dependent hyperphenylalaninemia due to deficiency of 6-pyruvoyl-
Mannitol
Microcrystalline cellulose
Ascorbic acid

6.8 Special precautions for storage

Keep the tightly closed in order to protect from moisture.

6.9 Nature and contents of the container

Nebulised tablets 100mg

6.10 MARKETING AUTHORISATION NUMBER

MTH-BH4 EU/1/0000015/14

7. DATE OF REVIE

Date of revision of the text: 10/2013

7.1 LIST OF REFERENCE