HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

4 February 2009

KUVAN 100 mg, soluble tablet
Box of 30 tablets (CIP: 390 462-4)
Box of 120 tablets (CIP: 390 463-0)

Applicant: MERCK LIPHA SANTE

sapropterin dihydrochloride

List I
Medicinal product for hospital prescription only

Orphan drug

ATC Code: A16AX07

Date of Marketing Authorisation (centralised procedure): 2 December 2008

Reason for request: inclusion on the list of medicinal products approved for use by hospitals.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sapropterin dihydrochloride[1]

1.2. Indications

"KUVAN is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and children aged four or over suffering from phenylketonuria (PKU) who have been shown to be responsive to such treatment.
KUVAN is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and children aged four or over with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment."

N.B.: Hyperphenylalaninaemia (HPA), which is an abnormal elevation of blood phenylalanine levels, is normally caused by autosomal recessive mutations of the genes coding for phenylalanine hydroxylase (in the case of PKU) or for the enzymes involved in the biosynthesis or regeneration of 6R-tetrahydrobiopterin (6R-BH4) (in the case of BH4 deficiency).
The aim of administering KUVAN to patients suffering from PKU who are responsive to BH4 is to boost the activity of the defective phenylalanine hydroxylase and, as a consequence, to increase or sufficiently restore the oxidative metabolism of phenylalanine in order to reduce or maintain blood phenylalanine levels, to prevent or reduce the build-up of phenylalanine and to increase tolerance of dietary phenylalanine.
The recommended blood phenylalanine levels for patients with PKU (µmol/l)[2] in France are:

Young children	Children	Adults
Age 0 - 10: 120-300	Age 10 - 18: < 900	Age over 18: 1,200-1,500

1.3. Dosage

"Treatment with KUVAN must be initiated and supervised by a physician experienced in the treatment of PKU and BH4 deficiency. KUVAN must be administered with a meal as a single daily dose, at the same time each day, preferably in the morning.
Active management of dietary phenylalanine and overall protein intake while taking KUVAN is required to ensure adequate control of blood phenylalanine levels and nutritional balance.
As HPA due to either PKU or BH4 deficiency is a chronic condition, once responsiveness to treatment is demonstrated, KUVAN is intended for long-term use. However, there are limited data regarding the long-term use of KUVAN.

Dosage:
KUVAN is provided as 100 mg tablets. The calculated daily dose based on body weight must be rounded up to the nearest multiple of 100. For example, a calculated dose of 401 to 450 mg must be rounded down to 400 mg, corresponding to 4 tablets. A calculated dose of 451 to 499 mg must be rounded up to 500 mg, corresponding to 5 tablets.
PKU

[1] sapropterin dihydrochloride is a synthetic form of sapropterin which can replace the endogenous chemical.
Sapropterin, or tetrahydrobiopterin (BH4), is a chemical produced by the body. Tetrahydrobiopterin is the cofactor of the aromatic amino acid hydroxylases, one of which is phenylalanine hydroxylase, an enzyme which enables phenylalanine to be converted into tyrosine.
[2] Abadie V, Berthelot J, Feillet F, et al. Consensus national sur la prise en charge des enfants dépistés avec une hyperphénylalaninémie [National consensus on the management of children found to be suffering from hyperphenylalaninaemia]. Arch Pediatr. 2005 ;12 :594-601

The starting dose of KUVAN in adults and children suffering from PKU is 10 mg/kg body weight once daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood phenylalanine levels as defined by the physician.

BH4 deficiency

The starting dose of KUVAN in adults and children with BH4 is 2 to 5 mg/kg body weight once daily. Doses can be adjusted up to 20 mg/kg/day. It may be necessary to divide the total daily dose into 2 or 3 administrations, distributed over the day, to optimise the therapeutic effect.

Determination of response:

It is of primary importance to initiate KUVAN treatment as early as possible to avoid the appearance of non-reversible clinical manifestations of neurological disorders in children and cognitive deficits and psychiatric disorders in adults due to sustained elevations of blood phenylalanine.

Response to treatment is determined by a decrease in blood phenylalanine following treatment with KUVAN. Blood phenylalanine levels should be checked before initiating treatment and after 1 week of treatment with KUVAN at the recommended starting dose. If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose of KUVAN can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels over a one-month period. The dietary phenylalanine intake must be maintained at a constant level during this period.

A satisfactory response is defined as a ≥30% reduction in blood phenylalanine levels or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. Patients who fail to achieve this level of response within the one-month test period must be considered non-responsive and may not receive treatment with KUVAN.

Once response to KUVAN has been established, the dose may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

It is recommended that blood phenylalanine and tyrosine levels be tested one or two weeks after each dose adjustment and monitored frequently thereafter. Patients treated with KUVAN must continue a restricted phenylalanine diet and undergo regular clinical assessment (such as monitoring of blood phenylalanine and tyrosine levels, dietary intake and psychomotor development).

Method of administration:

The tablets must be administered as a single daily dose with a meal (to improve absorption) and at the same time each day, preferably in the morning.

Patients must be warned not to swallow the desiccant capsule found in the vial.

The prescribed number of tablets must be placed in a glass or cup of water and stirred until dissolved. It may take a few minutes for the tablets to dissolve. The tablets can be crushed to make them dissolve faster. Small particles may be visible in the solution, but they will not affect the efficacy of the medicinal product. The solution must be drunk within 15 to 20 minutes.

For doses below 100 mg, one tablet must be dissolved in 100 ml of water and the volume of solution corresponding to the prescribed dose administered. An accurate measuring device with suitable graduations must be used to ensure administration of the appropriate volume of solution.

Adults

The prescribed number of tablets must be placed in a glass or cup containing 120 to 240 ml of water and stirred until dissolved.

Children

The prescribed number of tablets must be placed in a glass or cup containing up to 120 ml of water and stirred until dissolved.

Dose adjustment:
Treatment with KUVAN may decrease blood phenylalanine levels below the desired therapeutic level. Adjustment of the sapropterin dose or modification of dietary phenylalanine intake may be required to achieve and maintain blood phenylalanine levels within the desired therapeutic range.
Blood phenylalanine and tyrosine levels must be tested, particularly in children, one to two weeks after each dose adjustment and monitored frequently thereafter, under the direction of the treating physician.
If inadequate control of blood phenylalanine levels is observed during treatment with KUVAN, the patient's compliance with the prescribed treatment and diet must be reviewed before considering an adjustment of the KUVAN dose.
Discontinuation of KUVAN treatment must only be carried out under the supervision of a physician. More frequent monitoring may be required, as blood phenylalanine levels may increase. Dietary modification may be necessary to maintain blood phenylalanine levels within the desired therapeutic range.

Specific patient groups:
KUVAN has not been specifically studied in children under 4 years of age.
The safety and efficacy of KUVAN in patients aged over 65 have not been established. Caution must be exercised when prescribing to elderly patients.
The safety and efficacy of KUVAN in patients with kidney or liver failure have not been established. Caution must be exercised when prescribing to such patients."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

A	Alimentary tract and metabolism
A16	Other alimentary tract and metabolism products
A16A	Other alimentary tract and metabolism products
A16AX	Various alimentary tract and metabolism products
A16AX07	sapropterin

2.2. Medicines in the same therapeutic category
There is no medicinal product similar to KUVAN.

2.3. Medicines with a similar therapeutic aim
KUVAN is the only proprietary drug indicated for the treatment of hyperphenylalaninaemia.
The non-drug alternative is a controlled diet low in phenylalanine plus consumption of phenylalanine-free protein replacements.

3 ANALYSIS OF AVAILABLE DATA

The clinical development of sapropterin (KUVAN) is based on:

- 5 clinical studies into the treatment of phenylketonuria (PKU)
  - study PKU-001, an open-label phase II study carried out to identify patients responsive to treatment with KUVAN
  - study PKU-003, a double-blind, randomised phase III study versus placebo carried out to assess the efficacy of KUVAN in reducing blood phenylalanine levels after six weeks of treatment. This study included those patients in the PKU-001 study who had responded to treatment with KUVAN. This study was followed by a 22-week open-label monitoring period (study PKU-004)
  - study PKU-006, a double-blind, randomised phase III study versus placebo carried out to assess the tolerance of phenylalanine among patients who responded to treatment with KUVAN
  - study PKU-008, an open-label phase III study assessing long-term tolerance (this study has not yet been completed)

- one clinical study into the treatment of BH4 deficiency, assessing the efficacy and tolerance of KUVAN (study PKU-007, not yet completed).

This document will describe only those comparative studies which can be used to assess the medical benefit to patients (i.e. studies PKU-003 and PKU-006).

N.B.: EMEA has requested three post-marketing studies:
- a study on children aged from birth to 4 years of age to assess the pharmacokinetics, efficacy and tolerance of KUVAN in this age group,
- a study on children aimed at assessing the long-term efficacy of KUVAN (with a seven-year monitoring period) on neurocognitive functions and growth,
- a register to collect data on patients treated with KUVAN aged 4 and over. It is intended that this register will collect data on elderly subjects (with no upper age limit), pregnant women, patients with kidney or liver failure and data on growth and neurocognitive development in children.

3.1. Efficacy results

3.1.1. In phenylketonuria (PCU)

study PKU-003[3]

Aim: to assess the efficacy of KUVAN on reducing blood phenylalanine levels after 6 weeks treatment and its tolerance among patients with PKU

Methodology: multi-centre, double-blind, randomised, placebo-controlled phase III studies.
The patients included in this study (n=89) had previously taken part in the PKU-001 study which was carried out in order to identify patients responsive to treatment with KUVAN.

Response to treatment was defined as follows: patients were considered "responders" to treatment if their blood phenylalanine level fell by ≥ 30% after 8 days treatment with a fixed dose of KUVAN.
This definition does not establish a correlation with the absolute plasma phenylalanine, which is an important parameter in defining well-balanced management of patients with PKU and guaranteeing normal development.

Submission of the results of the PKU-001 study for information[4]
This is a phase II, multi-centre, open-label study on 490 patients with PKU (age ≥ 8, blood phenylalanine level ≥ 600 µmol/l in the case of patients recruited before amendment 2 to the protocol or ≥ 450 µmol/l in the case of patients recruited after amendment 2 to the protocol). The patients were treated with KUVAN at a dose of 10 mg/kg/day for 8 consecutive days and were monitored for 6 weeks. They were required to continue with their normal diet with no change in their phenylalanine intake.
The primary endpoint was response to treatment, defined as a fall of ≥ 30% in the blood phenylalanine level between D1 and D8.
485 patients had their blood phenylalanine levels measured on D1 and D8, and 96 of them (i.e. 20% of patients taking part, 95% CI [16%,23%]) were found to have a decrease of ≥ 30% in their blood phenylalanine levels at D8, meaning that they were classified as responding to the treatment.

Inclusion criteria

- age ≥ 8
- having taken at least 7 of the 8 doses they were scheduled to take in the PKU-001 study
- being a "responder" to KUVAN (see study PKU-001)
- having blood phenylalanine levels of ≥ 600 µmol/l in the case of patients recruited before amendment 2 to the protocol (n=19) or ≥ 450 µmol/l in the case of patients recruited after amendment 2 to the protocol (n= 70).

N.B.: the limit of 600 µmol/l had initially been chosen because it has been shown that patients' intellectual capacities were better when blood phenylalanine levels were ≤ 600 µmol/l[5]. It was finally decided to apply a threshold of 450 µmol/l in order to accelerate recruitment of patients matching the study population.

[3] Levy HL, Milanowski A, Chakrapani A, et al. Sapropterin Research Group. Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. Lancet. 2007;370:504-10.
[4] Burton BK et al. The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study. J Inherit Metab Dis. 2007;30(5):700-7.
[5] EMEA CHMP opinion (25/09/2008)

Dosing regimen:
Patients were randomised to receive either KUVAN at a dose of 10 mg/kg/day (n=42) or a placebo (n=47) for 6 weeks.
They did not follow a controlled low-phenylalanine diet.

Primary endpoint: change in blood phenylalanine levels after 6 weeks treatment.

Secondary endpoints:
- weekly change in blood phenylalanine levels during the 6 weeks of treatment
- percentage of patients with blood phenylalanine levels below 600 µmol/l after 6 weeks treatment.

Additional endpoint: compliance with treatment (assessed by counting the number of tablets left in the vial at each follow-up appointment).

Results (ITT population)
Baseline patient characteristics:
88 of the 89 patients included in the study received at least one dose of treatment (41 in the KUVAN group, 47 in the placebo group).

Table 1: baseline patient characteristics

Characteristics	Placebo N=47	KUVAN N=41	Total N=88
Gender, n (%) Male Female	24 (51) 23 (49)	27 (66) 14 (34)	51 (58) 37 (42)
Average age (years) ± standard deviation	19.5 ± 9.8	21.5 ± 9.5	20.4 ± 9.7
Age group, n (%) 8 – 12 > 12	11 (23) 36 (77)	6 (15) 35 (85)	17 (19) 71 (81)
Baseline blood phenylalanine levels (µmol/l ± standard deviation)	888.3 ± 323.1	842.7 ± 299.6	-

The characteristics of patients in both groups were similar on inclusion.

Results for the primary endpoint:

Table 2: blood phenylalanine levels during the 6 weeks of treatment

	Placebo (n=47)	KUVAN (n=41)
Blood phenylalanine level (µmol/l ± standard deviation)		
Baseline	888.3 ± 323.1	842.7 ± 299.6
Week 1	862.6 ± 345.6	619.9 ± 354.7
Week 2	863.2 ± 325.2	615.8 ± 340.2*
Week 4	906.9 ± 341.4	587.5 ± 375.5
Week 6	891.2 ± 347.6	606.9 ± 377.0
Change in blood phenylalanine level between baseline and the end of treatment		
Week 1	-25.7 ± 232.3	-222.9 ± 192.4
Week 2	-25.2 ± 260.9	-207.0 ± 273.2
Week 4	18.5 ± 239.5	-255.3 ± 248.4
Week 6	2.9 ± 239.5	-235.9 ± 257.0

*n=40

After 6 weeks treatment an average change in blood phenylalanine levels of -235.9 ± 257.0 µmol/l was observed in the KUVAN group and + 2.9 ± 239.5 µmol/l in the placebo group. The difference between the two groups was 245 ± 52.5 µmol/l (p<0.001).

Results for secondary endpoints:

- weekly change in blood phenylalanine levels during the 6 weeks of treatment (see table 2):

In the KUVAN group, the average blood phenylalanine level fell in the first week of treatment. In the placebo group, the average blood phenylalanine level fell after two weeks of treatment but was higher than at baseline by week four.

- percentage of patients with blood phenylalanine levels below 600 µmol/l after 6 weeks treatment:

The percentage of patients with a baseline blood phenylalanine level ≥ 600 µmol/l was 83% in the KUVAN group and 81% in the placebo group.
After 6 weeks of treatment, the percentage of patients with a blood phenylalanine level < 600 µmol/l was 54% in the KUVAN group versus 23% in the placebo group (p = 0.004).[6]

Treatment compliance:
During the study 72 patients (37 in the KUVAN group and 35 in the placebo group) took all the doses during the 6 weeks of treatment and 68 patients (32 in the KUVAN group and 36 in the placebo group) took all the treatment doses at the scheduled times. The average number of forgotten doses during the 6 weeks of treatment was 0.5 ± 2,4. Administration errors were rare. The average number of incorrect doses taken was 0.1 ± 0.3 and the average number of missing doses was 0.5 ± 2.4. The maximum number of forgotten doses was 3 in the KUVAN group and 21 in the placebo group.

study PKU-006

Aim: to assess the ability of KUVAN to increase phenylalanine tolerance in children aged between 4 and 12 suffering from PKU, responding to treatment and on a controlled low-phenylalanine diet.
Phenylalanine tolerance was measured by the average daily intake of phenylalanine in the diet or in the form of protein replacements.

Methodology: multi-centre, double-blind, randomised, placebo-controlled phase III study.

The study was conducted in two phases:

- Phase 1: identification of responsive patients

The patients were given a daily dose of 20 mg/kg of KUVAN (open-label), with monitoring appointments on D1 and D8. They were considered to be responders if:
- the decline in blood phenylalanine levels between D1 and D8 was ≥ 30%;
- their blood phenylalanine level at D8 was ≤ 300 µmol/l;

Responsive patients were then eligible for phase 2 of the study after a treatment-free interval of at least one week.

[6] After 6 weeks, 85% (35/41) of patients being treated with KUVAN had lower blood phenylalanine levels versus 57% (27/47) of patients taking placebo.
In the group of patients being treated with KUVAN and having lower blood phenylalanine levels, 54% (18/33) had a decrease of 30% or more versus 11% (5/47) in the placebo group.

- Phase 2: assessment of phenylalanine tolerance

The patients were randomised (3:1) to receive either KUVAN at a dose of 20mg/kg/day or a placebo for 10 weeks.
The protocol provided for stratified randomisation according to blood phenylalanine levels (<300 µmol/l or ≥300 µmol/l) in the 6 months prior to inclusion in phase 1. The patients were required to maintain their low-phenylalanine diet until the third week. They could then increase their phenylalanine intake depending on the blood levels observed.

Inclusion criteria

- 4 ≤ age to ≤ 12
- PKU diagnosis documented by at least one blood phenylalanine reading ≥ 360 µmol/l
- controlled low-phenylalanine diet defined by:
    - phenylalanine tolerance ≤ 1,000 mg/day,
    - an average blood phenylalanine level ≤ 480 µmol/l for at least 6 months prior to inclusion in the study

Primary endpoints:

► For phase 1 of the study: blood phenylalanine level at D8 and percentage of variation in blood phenylalanine level between D1 and D8
► For phase 2 of the study: increase in daily phenylalanine intake (supplements) in week 10, with blood phenylalanine levels remaining < 360 µmol/l.

Secondary endpoints for phase 2 of the study:

- difference between blood phenylalanine levels at week 0 and week 3, before the increase in phenylalanine intake,
- comparison of the additional amount of phenylalanine tolerated in week 10 in each group

Other criterion: compliance with treatment.

Results (ITT population)

Baseline patient characteristics:
90 patients were included in phase 1 and received at least one dose of KUVAN.
50 of these 90 patients (56%) were regarded as responders and were eligible for phase 2 of the study. 46 were randomised[7] to the KUVAN group (n=34) or the placebo group (n=12). One of the patients in the KUVAN group did not receive the treatment. This patient's results were not included in the analysis of the efficacy and tolerance data.

[7] the parents of 2 patients refused to have their child continue with the study, 1 patient was excluded by the investigator and 1 patient was not available to take part in the follow-up of the study.

Table 3: baseline characteristics of randomised patients

	Phase 1	Phase 2		
Characteristics	**Total N=50**	**Placebo N=12**	**KUVAN N=33**	**Total N=45**
Gender, n (%) Male Female	29 (58) 21 (42)	6 (50) 6 (50)	20 (61) 13 (39)	26 (58) 19 (42)
Average age (years) ± standard deviation	7.4 ± 2.5	7.1 ± 2.0	7.7 ± 2.8	7.5 ± 2.6
Blood phenylalanine level in the 6 months prior to the study n (%) - <300 µmol/l - ≥ 300 µmol/l	 25 (50) 25 (50)	 5 (42) 7 (58)	 17 (50) 17 (50)	
Baseline blood phenylalanine (µmol/l ± standard deviation)	298.7 ± 99.1	303.3 ± 74.4	314.1 ± 106.5	311.2 ± 98.3

It should be noted that baseline blood phenylalanine levels were close to the maximum recommended target figures for children aged 4 to 12 (300 µmol/l) and that 50% of the children recruited had a blood phenylalanine level of < 300 µmol/l.

Primary endpoint results:

► in phase 1: for all the responsive patients, blood phenylalanine levels fell from 317.0 ± 173.2 µmol/l to 108.1 ± 70.2 µmol/l between D1 and D8.

► in phase 2:

Table 4: additional amount of phenylalanine tolerated after 10 weeks treatment

Additional amount of phenylalanine tolerated (mg/kg/day)	**Placebo N=12**	**KUVAN N=33**
Total	2.9 ± 4.0 p=0.027	20.9 ± 15.4 p<0.001
Baseline blood phenylalanine level - <300 µmol/l - ≥ 300 µmol/l	 2.0 ± 4.5 (n=5) 3.6 ± 3.8 (n=7)	 24.7 ± 16.0 (n=16) 17.4 ± 14.5 (n=17)
Amount of phenylalanine tolerated, n (%) - 0 mg/kg/day - 1-10 mg/kg/day - 11-20 mg/kg/day - 21-30 mg/kg/day - 31-40 mg/kg/day - 41-50 mg/kg/day	 7 (58) 4 (42) 0 0 0 0	 5 (15) 7 (21) 8 (24) 2 (6) 8 (24) 3 (9)

In week 10, the average additional amount of phenylalanine allowing blood phenylalanine levels to be maintained < 360 µmol/l was 20.9 ± 15.4 mg/kg/day in the KUVAN group and 2.9 ± 4.0 mg/kg/day in the placebo group. As this is a comparison of the situation before treatment and the situation after treatment, no formal conclusions can be drawn from this result.

Results for the secondary endpoints in phase 2:
- difference between blood phenylalanine levels at week 0 and week 3, before the increase in phenylalanine intake:
The average change in blood phenylalanine levels in week 3 compared to baseline was -148.5 ± 134.2 µmol/l (p<0.001) in the KUVAN group and -96.6 ± 243.6 µmol/l in the placebo group (NS).

- comparison of the additional amount of phenylalanine tolerated in week 10 in each group:
At week 10, the average additional amount of phenylalanine tolerated was higher in the KUVAN group than in the placebo group. The respective figures were 21.0 ± 2.3 mg/kg/day and 3.3 ± 3.9 mg/kg/day (p<0.001).

Treatment compliance:
80% of the patients who received at least one treatment dose took all the doses correctly (85% of the patients taking KUVAN and 67% of the patients in the placebo group). Six patients forgot to take one or more treatment doses (2 patients in the KUVAN group and 4 in the placebo group).

3.1.2. In BH4 deficiency

No relevant clinical data is currently available for BH4 deficiency. A study (PKU-007) is being carried out at present.
The company presented a summary of the results of a phase II open-label study on 16 patients taking sapropterin dihydrochloride granules*, a post-marketing study conducted on 27 patients taking sapropterin dihydrochloride granules* who were monitored for 10 years and those of a study carried out in northern China between 1992 and 2005 on 27 patients with BH4 deficiency being treated with BH4 (at doses of 1 to 5 mg/kg/day).
** The marketing authorisation in France was granted for the tablet form*

As no comparative data is available, no conclusions can be drawn from these studies regarding the clinical benefits of KUVAN in BH4 deficiency.

3.2. Safety data

Tolerance data was obtained from four clinical studies (PKU-001, PKU-003, PKU-004, PKU-006). During these studies, 79.7% of patients (n=458) were treated with KUVAN for less than 10 days. 18.4% of patients (n= 106) received treatment for between 2 and 7 months.
1,052 adverse events were reported during the various studies: 1,045 were of slight or moderate intensity and 7 were of severe intensity.
5 patients suffered severe adverse events during the trials: headache (2), abdominal pain (1), diarrhoea (1), migraine (1), dental abscess (1) and vomiting (1).
Among the adverse effects observed in all the trials, headache and rhinorrhoea were very common (≥ 10% of patients), while diarrhoea, vomiting, abdominal pain, nasal congestion, pharyngolaryngeal pain and cough were less common (≥1% and < 10%).
No serious adverse effect was observed.
The SPC states that convulsions and exacerbation of convulsions have been observed in patients with BH4 deficiency taking a sapropterin product as part of a clinical study. This was not observed in clinical trials of KUVAN on patients with PKU.

3.3. Conclusion

The efficacy and tolerance of KUVAN (sapropterin dihydrochloride) have been assessed in 5 clinical studies into the treatment of phenylketonuria (PCU). This document only considers the comparative studies PKU-003 and PKU-006 which are likely to be useful in assessing the clinical benefit to patients.

No relevant clinical data is currently available for BH4 deficiency.

The aim of study PKU-003, a phase III double-blind randomised study versus placebo, was to assess the tolerance and efficacy of KUVAN for an intermediate criterion, reduction in blood phenylalanine levels after 6 weeks of treatment, in 89 patients aged over 8 suffering from PKU. The patients did not follow a controlled low-phenylalanine diet, which raises the problem of how far the data can be transposed since this study was not carried out under actual conditions of use. In fact, diet is the standard treatment for PKU, and the SPC recommends that "patients taking KUVAN must follow a low-phenylalanine diet."
After 6 weeks of treatment, the average change in the blood phenylalanine level (primary endpoint) was -235.9 ± 257.0 µmol/l in the KUVAN group and + 2.9 ± 239.5 µmol/l in the placebo group; the difference between the two groups was therefore 245 ± 52.5 µmol/l ($p<0.001$).

The aim of study PKU-006, a phase III double-blind randomised study versus placebo, was to assess the ability of KUVAN to increase phenylalanine tolerance in children aged between 4 and 12 suffering from PKU, responding to treatment and on a controlled low-phenylalanine diet. The study was carried out in two phases: an initial phase to identify responsive patients, and a second phase assessing tolerance to phenylalanine over a 10-week period.
In week 10, the average additional amount of phenylalanine tolerated (primary endpoint) was 20.9 ± 15.4 mg/kg/day in the KUVAN group and 2.9 ± 4.0 mg/kg/day in the placebo group. As this is a comparison of the situation before treatment and the situation after treatment, no conclusions can be drawn from this result.
One of the secondary endpoints (comparison between the additional amount of phenylalanine tolerated at week 10 in each group) is interesting. At week 10, the average additional amount of phenylalanine tolerated in the KUVAN group was 21.0 ± 2.3 mg/kg/day, compared to 3.3 ± 3.9 mg/kg/day in the placebo group ($p<0.001$).
This study did not show whether the increase in phenylalanine intake allowed patients to stop taking phenylalanine-free protein replacements without suffering nutritional deficiency. It also did not show a correlation between the average additional amount of phenylalanine tolerated and the exact amount of additional proteins that the patient was able to take.

As the aim of current management of patients suffering from PKU is to reach the blood phenylalanine levels defined by French recommendations, the percentage of patients achieving the target values would have been a clinically relevant primary endpoint. However, the patients included in the studies had plasma phenylalanine levels close to normal values.
The duration of these two studies was short in view of the fact that hyperphenylalaninaemia is a chronic condition.
No data for children under 4 is available. Most of the patients taking part in study PKU-003 were aged over 12. Study PKU-006 did include young children.
Patients' quality of life was not assessed.
No study including a controlled low-phenylalanine diet as a comparator has been carried out; a study of this kind would enable the contribution of KUVAN compared to conventional management to be quantified.
As no comparative data is available, no conclusions can be drawn regarding the clinical benefits of KUVAN in BH4 deficiency.

About 35% of the 579 patients who were treated with KUVAN in the context of clinical trials experienced adverse effects. The effects most often reported were headache and rhinorrhoea. Respiratory disorders (nasal congestion, cough), gastrointestinal disorders (diarrhoea, vomiting, abdominal pain), pharyngolaryngeal pain and one case of hypophenylalaninaemia were also observed.
A risk management plan to monitor gastrointestinal disorders, hypophenylalaninaemia, the rebound effect and drug interactions has been drawn up. This will also improve understanding of the tolerance of KUVAN in certain specific populations (pregnant women, children under 4, the elderly, people with kidney and liver failure).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Hyperphenylalaninaemia is a metabolic abnormality with two main causes: phenylketonuria and BH4 deficiency. Phenylketonuria, which is a hereditary metabolic condition, is characterised by mental retardation and serious neurological disorders if it is not treated in the first few weeks of life. BH4 deficiency is a very rare congenital abnormality with clinical signs that are more severe than those of phenylketonuria. If a pregnant woman has phenylketonuria which is not treated during pregnancy, her hyperphenylalaninaemia has a toxic effect on foetal development and causes severe embryofoetopathy.
This proprietary drug is intended to provide curative treatment.
Its efficacy/adverse effects ratio is high.
This medicinal product is for use as first-line treatment.
There is no alternative medication.

> Public health benefit:
> Hyperphenylalaninaemia (HPA) (in the case of PKU or of BH4 deficiency) is a serious disease that represents a low public health burden in view of its rarity (orphan disease).
> As improving care for orphan diseases is an identified priority (Rare Diseases Programme in particular), treatment for this condition is a public health need.
> A review of the data available shows that the impact expected of the proprietary drug KUVAN is difficult to quantify in patients in terms of morbidity, mortality and quality of life.
> There is no certainty that the proprietary drug KUVAN will meet the identified public health need.
> Accordingly, in the current state of knowledge, this proprietary drug is not expected to have an impact on public health.

The actual benefit is substantial.

4.2. Improvement in actual benefit

KUVAN offers a moderate Improvement in Actual Benefit (IAB III) in the management of hyperphenylalaninaemia in adults and in children aged 8 and above suffering from phenylketonuria, and in adults and children suffering from tetrahydrobiopterin (BH4) deficiency who have been identified as responding to this type of treatment.

4.3. Therapeutic use[8]

Neonates are screened for phenylketonuria (PKU) by phenylalaninaemia measurement. A positive result is followed by confirmation of the diagnosis at a centre specialising in the treatment of PKU. Appropriate therapeutic management for the type of PKU involved is initiated as soon as the diagnosis is confirmed. The distinction between typical and atypical groups[9] is important because the patients in each group do not have the same tolerance of

[8] Feillet F. La phénylcétonurie. [Phenylketonuria] Encyclopédie Orphanet. [Orphanet encyclopaedia] March 2006

[9] HPA has been classified on the basis of blood phenylalanine levels:
typical PKU: blood phenylalanine ≥1,200 µmol/l
atypical PKU: blood phenylalanine between 600 and 1,200 µmol/l
These two forms require a controlled restricted diet.
moderate HPA: blood phenylalanine level between 120 and 599 µmol/l; in this case no special products need to be included in the diet.

phenylalanine in their diet and do not have the same level of response to pharmacological doses of BH4.
The aim of current management of patients suffering from PKU is to achieve acceptable blood phenylalanine levels as defined in the French recommendations (see table on page 2).
Current management of hyperphenylalaninaemia is limited to strict imposition of a controlled low-phenylalanine diet. Patients on this diet must take phenylalanine-free protein substitutes to ensure that they have a sufficient intake of essential amino acids.
Some patients on a phenylalanine-controlled diet can lead a practically normal life provided that they accept and comply with their diet. The diet imposes constraints on patients and their families, but is perfectly feasible for many patients not suffering from a nutritional deficiency. However, the severe constraints associated with this diet can make it difficult for patients to comply with it, especially during adolescence.
Strict metabolic control is vital in the first ten years of life, after which the diet is gradually made less restricted. Pregnant women must return to the restricted diet in order to avoid phenylketonuric embryofoetopathy.
Management is primarily on an individual basis.

Therapeutic use of KUVAN:
KUVAN is a new way of treating patients suffering from hyperphenylalaninaemia. It is the only drug currently indicated for the treatment of hyperphenylalaninaemia that can bring down a patient's plasma phenylalanine level. However, it is not effective in all patients. Moreover, in most cases it cannot of itself achieve normal plasma phenylalanine levels. It allows better control of plasma phenylalanine levels and means that patients can have a higher dietary intake of phenylalanine. KUVAN must be used in combination with a strictly controlled phenylalanine diet.
This drug treatment could improve compliance with therapy as it allows patients' phenylalanine tolerance to increase and so enables patients (particularly adolescents) to eat a more varied diet. This is important as it is during adolescence that patients start to resent the strict nature of their diet which has quite a severe psychological impact over the longer term.
KUVAN would offer the advantage of relaxing the diet and allowing patients who respond to treatment and find the diet onerous to reduce their intake of amino acid replacements or even stop taking them altogether.
This product will not benefit patients who accept the diet.
Management of patients must be individual and take account of the benefits of a less restrictive diet.
This drug must not be administered to children under the age of 4 as part of the management of hyperphenylalaninaemia caused by PKU since this use has not yet been assessed.
Long-term monitoring is very important as the status after the age of forty of patients correctly treated in childhood is not yet known.

4.4. Target population[10]

KUVAN is indicated for the treatment of adults and children aged over 4 suffering from hyperphenylalaninaemia caused by phenylketonuria and of adults and children suffering from hyperphenylalaninaemia caused by BH4 deficiency who respond to the treatment.
The incidence of BH4 deficiency is low (1 to 2% of all cases of hyperphenylalaninaemia)[11].
In France, the incidence of phenylketonuria is 1/17,000, with around 50 new cases being diagnosed each year[12].

[10] Feillet F. La phénylcétonurie. [Phenylketonuria] Encyclopédie Orphanet. [Orphanet encyclopaedia] March 2006
[11] In 2007, 561 patients were listed on the international register of patients suffering from BH4 deficiency. Half of the cases were in Europe.
[12] Abadie V. et al. Neonatal screening and long-term follow-up of phenylketonuria : the French database. Early Hum Dev 2001; 65: 149-58

Health insurance data indicates that phenylketonuria is the most common monogenic hereditary metabolic disease in France, with a population estimated at 800 patients in 2005[13].
Patients are considered responsive to treatment with KUVAN if their blood phenylalanine level decreases by 30% or more after 8 days treatment.
During clinical studies, the rate of response to treatment varied between 20 and 56% depending on the dose administered. However, this result is probably an overestimate given the biases in these studies. The experts estimate that the population of patients with phenylketonuria who could benefit from this drug is around 30% of people with atypical phenylketonuria and less than 10% of patients with typical phenylketonuria, or around 30% of all patients.
Given that the population in 2005 was 800 patients, the number of patients who might respond to treatment with KUVAN would be around 240. However, only patients aged over 4 are eligible for treatment.
According to INSEE data[14], 5% of the total population is under the age of 4.

This means that the target population for KUVAN would be around 230 patients.
This is a theoretical estimate of the target population. In practice, responsive patients will be treated with KUVAN when they start to find it hard to accept the strictness of the diet and when the psychological impact of the diet, which is quite restrictive over the long term, becomes severe.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the indication and at the dosage given in the marketing authorisation.

[13] Plan pour l'amélioration de la qualité de vie des personnes atteintes de maladies chroniques. [Plan for improving the quality of life of people suffering from chronic diseases] 2007-2011. Ministry of Health and Solidarity. April 2007
[14] INSEE: total population by age and sex as of 1 January 2008, the whole of France.