HAUTE AUTORITÉ DE SANTÉ

**The legally binding text is the original French version**

# TRANSPARENCY COMMITTEE

## Opinion

## 23 July 2014

## NORMOSANG, 25 mg/ml, concentrate for solution for infusion

**Box of 4 vials (CIP: 34009 558,611 1 9)**

Applicant: Orphan Europe

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| INN | Human hemin (hematin) |
| ATC Code (2012) | B06AB01 (other haematological medicinal products) |
| Reason for the review | **Re-assessment of the IAB following joint referral from the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services on 10 October 2013, in accordance with article R 163-19 of the French Social Security Code.** |
| List concerned | **Hospital use (French Public Health Code L.5123 2)** |
| Indication concerned | **"Treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)"** |

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| **Actual Benefit** | **The actual benefit of NORMOSANG® is substantial.** |
| **Improvement in Actual Benefit** | **NORMOSANG, the only available medicinal product based on human hemin, provides a substantial improvement in actual benefit (Level II) in the treatment of severe acute attacks of hepatic porphyria.** |
| **Therapeutic Use** | NORMOSANG is a first-line treatment in the management of severe acute attacks of hepatic porphyria. |
| **Recommendation** | Favourable opinion to continuation of reimbursement. |

# 01 ADMINISTRATIVE AND REGULATORY INFORMATION

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| Marketing Authorisation (mutual recognition) | Initial date: 5 May 1995 (Reference Member State: France) |
| Prescribing and dispensing conditions/special status | List I<br>Use in hospitals only |
| ATC Classification | 2012<br>B Blood and blood-forming organs<br>B06 Other haematological agents<br>B06A Other haematological agents<br>B06AB Other haematological products<br>B06AB01 Hematin |

# 02 BACKGROUND

As part of the work aimed at updating the list of chargeable medicinal products in addition to hospital services by the Hospitalisation council, and pursuant to article R 163-19 of the French Social Security Code, the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services has applied to HAS for a ruling on the IAB of proprietary medicinal products, including **NORMOSANG 25 mg/ml, concentrate for solution for infusion**, subject of this opinion.
Due to the length of inclusion, starting during a time when the IAB was not part of the assessment as it is today, this criterion had not been assessed by the Committee.

In the inclusion opinion (opinion on 28/11/1995), the Committee considered that: *"In a group of rare but debilitating and sometimes fatal diseases, the therapeutic benefit of NORMOSANG is clearer the earlier the treatment is started. The effect of the treatment on abdominal pains appears constant. Early initiation of treatment appears to prevent the occurrence of neurological complications. "*

# 03 THERAPEUTIC INDICATION

"Treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)"

# 04 DOSAGE

"The recommended daily dose is 3 mg/kg once daily for four days, diluted in 100 ml of 0.9% sodium chloride in a glass bottle and infused intravenously over at least 30 minutes into a large antebrachial or central vein using an inline filter.
The dose should not exceed 250 mg (1 ampoule) per day.
Exceptionally, the course of the treatment may be repeated under strict biochemical surveillance if there is inadequate response after the first course of treatment. "

Elderly patients: No dose adjustment is required.

Children and adolescents: Attacks of porphyria are rare in children but limited experience in tyrosinaemia suggests that it is safe to use a dose of not more than 3 mg/kg daily for 4 days, administered with the same precautions as for adults. "

# 05 THERAPEUTIC NEED[1,2]

Acute hepatic porphyria is a rare genetic disease (monogenic, autosomal and dominant inheritance) which can lead to the onset of severe, sometimes irreversible and potentially fatal neurological symptoms.

Acute hepatic porphyria includes four diseases:
- acute intermittent porphyria (AIP; the most common),
- porphyria variegata (PV),
- hereditary coproporphyria (HC),
- inherited deficiency of delta-aminolevulinic acid dehydratase (ALAD deficiency; rare).

Acute hepatic porphyria is caused by a deficiency of one of the enzymes from the haem biosynthesis pathway resulting in an accumulation of porphyrin precursors in the liver (delta-aminolevulinic acid, ALA and porphobilinogen, PBG) and also, in the case of PV and HC, in the cutaneous tissues. The accumulation of the porphyrin precursors (ALA and PBG) causes acute attacks while excess porphyrins results in hypersensitivity to sunlight and cutaneous signs of porphyria.

Diagnosis is based on the detection of elevated concentrations of ALA and, especially, PBG which is pathognomonic, and, sometimes, porphyrins in the urine, faeces or plasma. The type of porphyria is defined through enzyme measurements, then characterisation of the mutations on the corresponding DNA.

Each disease is different but they all share a common risk of occurrence of "acute attacks of porphyria" (neurological and visceral attacks) which are manifested by non-specific clinical signs such as intense abdominal pains and neuropsychiatric disorders which can be at the origin of serious emergencies and prolonged hospitalisation.

The attacks are most often triggered by exogenous factors (porphyrinogenic medicinal products, alcohol, infections, prolonged fasting or low calorie diet, stress, emotional shock) and/or endogenous (hormonal, linked to the menstrual cycle).

Management of porphyria includes the prevention of attacks (avoiding triggering factors), protection of the skin from light in the case of cutaneous signs and management of pain.

When a severe acute attack is confirmed, its treatment with human hemin (NORMOSANG) injection and/or infusion of carbohydrates becomes a therapeutic emergency.
In some patients, the attacks can be recurrent, requiring repeated injections of human hemin with short intervals between injections. They are thus debilitating and can lead to a possible indication for a liver transplant.

**1.1.** In this context, NORMOSANG (human hemin) represents a first-line treatment in the management of severe acute attacks of porphyria.

[1] www.orphanet.fr.
[2] http://www.sante.gouv.fr/les-porphyries-aigues-hepatiques.html.

# 06 CLINICALLY RELEVANT COMPARATORS

NORMOSANG is the only proprietary medicinal product based on human hemin available on the market.

### Conclusion

There is no relevant comparator for NORMOSANG.

# 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

NORMOSANG is available in the following countries: Germany, Austria, Belgium, Cyprus, Colombia, Denmark, Spain, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Netherlands, Poland, Portugal, Czech Republic, UK, Russia, Slovakia, Slovenia, Sweden.

# 08 SUMMARY OF PREVIOUS ASSESSMENTS

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| **Date of opinion** | 28/11/1995<br>Inclusion on the list of medicines approved for hospital use |
| **Indication** | Treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria).<br>It is important to warn the patient about the risks of worsening or triggering of attacks by fasting and the use of certain medicinal products. |
| **AB (wording)** | Not defined |
| **IAB (wording)** | In a group of rare but debilitating and sometimes fatal diseases, the therapeutic benefit of NORMOSANG is clearer the earlier the treatment is started. The effect of the treatment on abdominal pains appears constant. Early initiation of treatment appears to prevent the occurrence of neurological complications. |

# 09 ANALYSIS OF AVAILABLE DATA

The efficacy and safety data for NORMOSANG (human hemin) in the treatment of acute attacks of hepatic porphyria provided by the applicant are based on:

- A review of clinical data assessed as part of the initial inclusion application for this proprietary medicinal product (opinion of the Committee on 28/11/1995).
- Three new literature references:
    - An open-label, single-centre study (AZ66) performed in the USA (Anderson et al. Unpublished) the objective of which was to evaluate the efficacy in terms of reducing symptoms, levels of delta-aminolevulinic acid (ALA), porphobilinogen and hospitalisation duration through the administration of haem arginate 3 mg/kg/day for 4 days in 10 patients experiencing an attack of hepatic porphyria.
    - An open-label, single-centre study performed in Sweden (Sardh et al. 2009[3]) in 3 patients, which will not be detailed in this opinion due to the methodology.
    - A retrospective analysis of 25 patients (112 attacks) monitored in South Africa (Hift et al. 2005[4]).

## 09.1 Efficacy

### 9.1.1 Review of available data

The inclusion application file (opinion on 28/11/1995) contained 22 studies including 237 patients and 17 healthy volunteers (see appendix 1) of which:

- one was a randomised, double-blind, crossover versus placebo study performed in Ireland on nine patients,
- one was a French study comparing NORMOSANG with haem preparations in five patients,
- several were open-label international studies.

Based on this data, the Transparency Committee concluded:
**"Analysis of trials and comparative data:**

**Efficacy:** There is only one double-blind, randomised versus placebo study in which the low number of included patients (12) does not allow a significant conclusion to be drawn.
Several open-label studies including a low number of patients have been published. Given the experience acquired with other preparations, the treatments generally included a series of daily infusions for 4 days with active ingredient doses of 2-5 mg/kg of weight. All studies revealed an effect on urine elimination of the precursors (ALA and PBG). Even though the evaluation of clinical efficacy comes up against difficulties linked to the rarity of the disease and the extremely polymorphic presentation of the clinical signs, these studies reveal an accelerated curing of the acute abdominal attacks. No nephropathy occurred on treatment.

The product **safety** is generally good, subject to respecting the recommended administration conditions, however with a risk of possible occurrence of thrombophlebitis. This risk is estimated at less than 1% of 1000 identified administrations of NORMOSANG.

Given the origin of the preparation, the risk of transmission of infectious agents cannot be definitively excluded, neither can contamination by pathogens the nature of which is as yet unknown.

[3] Sardh E, Harper P, Andersson DE, Floderus Y. Plasma porphobilinogen as a sensitive biomarker to monitor the clinical and therapeutic course of acute intermittent porphyria attacks. Eur J Intern Med 2009; 20: 201-7.
[4] Hift R, Meissner P. An analysis of 112 acute porphyric attacks in Cape Town, South Africa. Medicine 2005 84; 1: 48-60

In any event, it is recommended that NORMOSANG is used in hospital departments with experience of managing patients with porphyria.

Therapeutic benefit:
In a group of rare but debilitating and sometimes fatal diseases, the therapeutic benefit of NORMOSANG® is clearer the earlier the treatment is started. The effect of the treatment on abdominal pains appears constant. Early initiation of treatment appears to prevent the occurrence of neurological complications. "

### 9.1.2 Study AZ66

Method: phase III, open-label study evaluating the efficacy of haem arginate 3 mg/kg/day for 4 days in 10 patients experiencing attacks of hepatic porphyria; continuation of treatment for 7 days was possible.

Inclusion criteria: Adult patients with acute intermittent porphyria, porphyria variegata, hereditary coproporphyria

- documented by laboratory parameters (elevation of aminolevulinic acid (ALA) and porphobilinogen):
    - o > 40 mg/day or 40 mg/l or a positive Watson-Schwartz test or Hoesch test for acute intermittent porphyria,
    - o > 10 mg/day or 10 mg/l or a positive Watson-Schwartz test or Hoesch test for porphyria variegata, hereditary coproporphyria.
- with clinical symptoms (severe abdominal pains, requiring strong analgesics) during the 7 days prior to inclusion (preceded by a period of 2 weeks without symptoms).
- and the presence of one of the following symptoms: nausea, vomiting, constipation, extremity pain, tachycardia (HR > 100 bpm), hypertension, peripheral neuropathy, ileus, dehydration, hyponatraemia.

Non-inclusion criteria, in particular: other cause of porphyria, normal level of urinary porphobilinogen, chronic or subacute symptoms (presenting for more than 2 weeks), history of treatment with a preparation containing haem, haemorrhagic disorders, etc.

Treatment: haem arginate 3 mg/kg/day for 4 days (n=10), with possibility of continuing the treatment for 7 days.

Primary efficacy endpoints:

- change in the levels of urinary ALA and urinary and serum porphobilinogen compared with the inital value measured over 24 hours every day and 3 days after cessation of treatment. The analysis was performed by ANOVA. If the effect of time was significant, a multiple comparison procedure was performed with Tukey's test. For the analysis of urinary concentrations of delta-aminolevulinic acid, a logarithmic transformation was required thus enabling the mean difference between the different days to be estimated. Due to the missing data, a secondary analysis was conducted to estimate the urinary porphobilinogen/urinary creatinine ratio and urinary delta-aminolevulinic acid/urinary creatinine ratio.
- changes in the symptoms of the porphyria attacks (severe abdominal pains and other pains requiring strong analgesics and other symptoms described below) evaluated with a severity scale[5] in comparison with the initial score. The symptom improvement rate was analysed with Cochran-Mantel-Haenszel analysis.

Number of subjects required and statistical analysis:

[5] 0: no symptoms, 1: easily tolerated (mild), 2: tolerated with difficulty (discomfort), 3: very poorly tolerated (painful), 4: intolerable (horrible), 5: worst (unbearable).

Since acute attacks of hepatic porphyria are rare events, the number of patients to be included is estimated at 20 subjects.
The threshold value for considering a statistically significant difference was fixed at α=0.05 with a bilateral test.

RESULTS: ITT analysis
A total of 10 patients were included in the analysis, 9 of which were women.
The average age was 41.6±11.8 years with an average weight of 64.9±22.2 kg. All patients had been diagnosed with acute intermittent porphyria apart from one patient (non-specific acute porphyria).

The urine was collected over 24 hours for four patients. Urine collection over a period of 9 to 12.33 hours was performed in three patients. Three patients started treatment after having given a urine sample.

- Urinary delta-aminolevulinic acid (mg/24 hours)

After 4 days of treatment with NORMOSANG, a reduction of the urinary ALA concentration was observed in comparison with the initial level: median level at inclusion 24.5 mg/24 hours [13.3 ; 79.2] and 2.4 mg/24 hours [1.9 ; 7.8] after 4 days of treatment, p=0.0001.

- Urinary porphobilinogen (mg/24 hours)

After 4 days of treatment with NORMOSANG, a reduction of the urinary porphobilinogen concentration was observed in comparison with the initial level: mean level at inclusion 74.53 mg/24 hours [11.8; 18.7] and 10.4 mg/24 hours [1.2 ; 29.7] after 4 days of treatment, p=0.020.

- Serum concentration of porphobilinogen (µg/ml)

After 4 days of treatment with NORMOSANG, a reduction of the serum porphobilinogen concentration was observed in comparison with the initial level: mean level at inclusion 1.595 µg/ml [0.519; 4.962] and 0.470 µg/ml [0.015 ; 1.702] after 4 days of treatment, p=0.0001.

- Changes in the porphyria symptoms

Concerning the different painful symptoms, a significant reduction between the score at inclusion and the score after 4 days of treatment was reported for:
- abdominal pains: median pain score[5] at inclusion of 3 versus 0 after 4 days of treatment (p≤0.05),
- other pains: median pain score[5] at inclusion of 2 versus 1 after 4 days of treatment (p=0.017),

### 9.1.3 Hift study 2005[4]

Descriptive analysis of 112 cases of acute attacks of porphyria (n=25) observed in a hospital in South Africa over a period of 14 years.
Haem arginate (NORMOSANG) was used in 75 cases (67%) and, according to the authors, this rapidly reduced the severity score of the symptoms (median resolution of symptoms was 6 days).
Given the methodology of this analysis, the results cannot be interpreted.

## 09.2 Adverse effects

### 9.2.1 Data from clinical studies

In the AZ66 study, 43 adverse events were observed in 10 patients. The most commonly observed events were:
- injection site pain or reaction (3), all considered to be related to the treatment,

- gastrointestinal disorders (abdominal pains (1), constipation (2), diarrhoea (2) and nausea (2)) 2 of which were considered to be related to the treatment,
- vascular disorders (deep vein thrombosis and phlebitis) one of which was considered to be related to the treatment.

In addition, 2 deaths were observed during this study.

### 9.2.2 PSUR data

During the period from 1 June 2010 to 31 May 2013 covered by the last periodic pharmacovigilance report (PSUR), 9769 boxes of NORMOSANG, corresponding to 9769 cycles of treatment were used and no new major adverse event has been reported.
Since MA was granted in 1995, 544 adverse events have been reported, 192 of which were serious (146 not listed). The most common events were "injection site reactions" and "vascular damage".
In total, three fatal cases have also been reported but considered not to be related to the treatment.

Following an inspection by an English agency (Medicines and Healthcare products Regulatory Agency (MHRA)), clarifications on the risk of venous thrombosis were requested. Therefore, as part of a type II variation, additions were requested specifying that cases of venous thrombosis in the vena cava and major tributaries (iliac and subclavian veins) have been observed. Validation of the new SPC is ongoing with the ANSM (French National Agency for Medicines and Health Products Safety).

### 9.2.3 SPC data

According to the SPC, "the most commonly reported ADRs are injection site reaction especially occurring if infusion takes place into veins which are too small" as well as vascular disorders (venous network alterations).

## 09.3 Summary & discussion

The efficacy and safety data for NORMOSANG (human hemin) in the treatment of acute attacks of hepatic porphyria provided by the company are based on a review of clinical data assessed as part of the initial inclusion application for this proprietary medicinal product (Committee opinion on 28/11/1995) and new literature data.

**Primary efficacy data**

Reminder of the conclusions of the previous opinion in 1995: *"There is only one double-blind, randomised versus placebo study in which the low number of included patients (12) does not allow a significant conclusion to be drawn.*
*Several open-label studies including a low number of patients have been published. Given the experience acquired with other preparations, the treatments generally included a series of daily infusions for 4 days with active ingredient doses of 2-5 mg/kg of weight. All studies revealed an effect on urine elimination of the precursors (ALA and PBG). Even though the evaluation of clinical efficacy is hampered by difficulties linked to the rarity of the disease and the extremely polymorphic presentation of the clinical signs, these studies reveal an accelerated curing of the acute abdominal attacks. No nephropathy occurred on treatment."*

In the open-label, single-centre study (AZ66) after 4 days of treatment in 10 patients with an attack of hepatic porphyria, significant reductions of urinary ALA and porphobilinogen over 24 hours, serum porphobilinogen and painful symptoms were observed in comparison with the initial level:

- urinary concentration of ALA: median value at inclusion 24.5 mg/14 hours [13.3 ; 79.2] and 2.4 mg/24 hours [1.9 ; 7.8] after 4 days of treatment, p=0.0001.

- urinary concentration of porphobilinogen: mean value at inclusion 74.53 mg/24 hours [11.8; 18.7] and 10.4 mg/24 hours [1.2 ; 29.7] after 4 days of treatment, p=0.020.
- serum concentration of porphobilinogen: mean value at inclusion 1.595 µg/ml [0.519; 4.962] and 0.470 µg/ml [0.015 ; 1.702] after 4 days of treatment, p=0.0001.
- abdominal pains: median pain score[5] at inclusion of 3 versus 0 after 4 days of treatment (p≤0.05),
- other pains: median pain score[5] at inclusion of 2 versus 1 after 4 days of treatment (p=0.017),

A retrospective analysis of 25 patients (112 attacks) monitored in South Africa (Hift et al. 2005[6]), haem arginate (NORMOSANG) was used in 75 cases (67%) and, according to the authors, this rapidly reduced the score of severity of the symptoms (median resolution of symptoms was 6 days). Given the methodology of this analysis, the results cannot be interpreted.

**Primary safety data:**
According to the SPC, "the most commonly reported ADRs are injection site reactions especially occurring if infusion takes place into veins which are too small" as well as vascular disorders (venous network alterations).
These adverse events are those which are also the most commonly observed in the available studies.

It should be noted that, as part of a type II variation, additions were requested specifying that cases of venous thrombosis in the vena cava and major tributaries (iliac and subclavian veins) have been observed and they are currently undergoing validation by the ANSM.

**Discussion:**
Due to the rarity of the disease and the extremely polymorphic clinical presentation, the available data are based on clinical studies with a low level of evidence.

Nevertheless, NORMOSANG is the only medicinal product based on human hemin available with MA on the French market.

## 09.4 Planned studies

The company has not reported any studies, either in progress or to come.

[6] Hift R, Meissner P. An analysis of 112 acute porphyric attacks in Cape Town, South Africa. Medicine 2005 84; 1: 48-60.

# 010 THERAPEUTIC USE[1,2]

The management of acute hepatic porphyria includes the prevention of attacks (avoiding exogenous triggering factors (porphyrinogenic medicinal products, alcohol, infections, prolonged fasting or low calorie diets, stress, emotional shock) and/or endogenous triggering factors (hormones, linked to the menstrual cycle) and the protection of the skin from light in cases with cutaneous signs.

When a severe acute attack is confirmed, its treatment with human hemin (NORMOSANG) injection and/or infusion of carbohydrates becomes a therapeutic emergency.

In some patients, the attacks can be recurrent, requiring repeated injections of human hemin with short intervals between injections. They are thus debilitating and can lead to a possible indication for a liver transplant.

**Role of NORMOSANG in the therapeutic strategy:**
NORMOSANG (human hemin) is the only medicinal product based on human hemin currently available on the market. In this context, it represents the reference treatment to be offered as a first-line treatment in the management of severe acute attacks of porphyria.

# 011 TRANSPARENCY COMMITTEE CONCLUSIONS

**In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:**

## 011.1 Actual benefit

◗ Acute hepatic porphyria is a rare genetic disease (monogenic, autosomal and dominant inheritance) which can lead to the onset of severe, sometimes irreversible and potentially fatal neurological symptoms. They are characterised by the risk of occurrence of "acute attacks of porphyria" (neurological and visceral attacks) which are manifested by non-specific clinical signs such as intense abdominal pains and neuropsychiatric disorders which can be at the origin of serious emergencies and prolonged hospitalisation.

◗ NORMOSANG 25 mg/ml, medicinal product based on human hemin, represents a replacement therapy for acute attacks of hepatic porphyria.

◗ Its efficacy/adverse effects ratio in the treatment of acute attacks of hepatic porphyria is substantial.

◗ There are no treatment alternatives.

◗ NORMOSANG is a first-line therapy.

◗ Public health benefit:
Given the rarity of the acute attacks of hepatic porphyria, the disease burden is low. Improvement in the management of orphan diseases is part of the Plan National Maladies Rares [National Rare Diseases Plan] 2011 2014, so the treatment of this disorder is a public health need.
According to the clinical data available, there is a treatment impact in terms of reduction of the ALA and porphobilinogen levels.

Its expected impact on quality of life has not been documented and cannot be quantified.

Especially due to the rarity of this condition, it is not expected that NORMOSANG will impact public health.

**Consequently, the Committee considers that the actual benefit of NORMOSANG 25 mg/ml is substantial in the Marketing Authorisation indication.**

**The Committee recommends maintenance of inclusion on the list of medicines approved for use by hospitals in the indication "treatment of acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)" and at the dosages in the Marketing Authorisation.**

## 011.2 Improvement in actual benefit (IAB)

**NORMOSANG, the only available medicinal product based on human hemin, provides a substantial improvement in actual benefit (level II) in the treatment of severe acute attacks of hepatic porphyria.**

## 011.3 Target population

The target population for NORMOSANG is represented by patients with acute attacks of hepatic porphyria (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria). It can be estimated on the basis of the following factors:

According to the Orphanet data,[1] in the majority of European countries, the prevalence of acute hepatic porphyria is around 1/75,000 which, in relation to the French population, would represent around 800 patients amongst which, depending on the French reference centre, 88% are in remission, 5% have relapsing attacks (1 to 4 attacks per year) and 7% are considered as recurrent (more than 4 attacks per year, which is 43 patients in France).

**Estimate:**
Consequently, the target population of NORMOSANG can be estimated at a maximum of 800 patients with 5 to 20 new patients per year.

# 012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

### ◗ Packaging
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.

# APPENDIX 1

## Reminder of the studies provided during the initial inclusion application

| | |
|---|---|
| Study 1 | Tenhunen R, Tokola O and Linden I B; Haem arginate: a new stable haem compound. J Pharm Pharmacol 1987; 39(10): 780-6 |
| Study 2 | Tokola O, Tenhunen R, Volin L*, et al.*; Pharmacokinetics of intravenously administered haem arginate. Br J Clin Pharmac 1986; 22(3): 331-5 |
| Study 3a | Volin L, Ruutu T, Knuutila S*, et al.*; Heme arginate treatment for myelodysplastic syndromes. Leukemia Research 1988; 12(5): 423-31 |
| Study 3b | Volin L; Haem arginate treatment for hereditary sideroblastic anaemia. Eur J Haematol 1989; 42: 60-66 |
| Study 4 | Volin L, Rasi V, Vahtera E*, et al.*; Heme arginate: effects on hemostasis. Blood 1988; 71(3): 625-628 |
| Study 5 | Study n° 15-110-87107.<br>Viljanen MK, Osterman T, Volin L, Kleimola T. Assessment of immunogenity of Normosang infusion preparation. Leiras, Study Report 1063, 1987. |
| Study 6 | Mustajoki P, Tenhunen R, Tokola O*, et al.*; Haem arginate in the treatment of acute hepatic porphyrias. Br Med J (Clin Res Ed) 1986; 293(6546): 538-9 |
| Study 7a | Kordac V and Martasek P; Haem arginate in acute hepatic porphyrias [letter]. Br Med J (Clin Res Ed) 1986; 293(6554): 1098 |
| Study 7b | Kordac V, Kozakova M and Martasek P; Changes of myocardial functions in acute hepatic porphyrias. Role of heme arginate administration. Ann Med 1989; 21(4): 273-276 |
| Study 8a | Du Mayne JFD, Deybach JC, Phung L, *et al.*; Crises aigues de porphyries hépatiques. Traitement par l'hematine cinq observations. La Presse Médicale 1986; 15: 1673-6 |
| Study 8b | Leiras Study Report, 1990, by Nordmann Y:<br>Treatment of Acute crises of Porphyrias by Heme-arginate (NORMOSANG®). |
| Study 9 | Leiras Study Report n° 1075:<br>Ruhle H; Final Report of a Clinical Study with NORMOSANG® in patients with acute intermittent porphyria. |
| Study 10a | Leiras Study Report, 1987:<br>Kostrzewska E, Heme-arginate (Normosang®) in porphyria. |
| Study 10b | Kostrzewska E, Gregor A and Tarczynska-Nosal S; Heme arginate (Normosang) in the treatment of attacks of acute hepatic porphyrias. Materia Medica Polona 1991; 23(4): 259-62 |
| Study 11 | Herrick A, McColl K E, McLellan A*, et al.*; Effect of haem arginate therapy on porphyrin metabolism and mixed function oxygenase activity in acute hepatic porphyria. Lancet 1987; 2(8569): 1178-1179 |
| Study 12 | Tokola O, Mustajoki P and Himberg J J; Haem arginate improves hepatic oxidative metabolism in variegate porphyria. Br J Clin Pharmac 1988; 26(6): 753-757 |
| Study 13 | Herrick A L, McColl K E, Moore M R*, et al.*; Controlled trial of haem arginate in acute hepatic porphyria [see comments]. The Lancet 1989; 1(8650): 1295-1297 |
| Study 14 | Herrick A L, McColl K E, Moore M R*, et al.*; Acute intermittent porphyria in two patients on anticonvulsant therapy and with normal erythrocyte porphobilinogen deaminase activity. Br J Clin Pharmac 1989; 27(4): 491-7 |
| Study 15 | Fitzsimmons E, Houston T, Cavill I*, et al.*; Erythropoiesis and Haem Biosynthesis in Hepatoerythropoietic Porphyria. Seminar Abstract, 1988, Glasgows, U.K 1988 |
| Study 16 | Timonen K, Mustajoki P, Tenhunen R*, et al.*; Effects of haem arginate on variegate porphyria. Br J Dermatol 1990; 123(3): 381-387 |
| Study 17 | Timonen T T and Kauma H; Therapeutic effect of heme arginate in myelodysplastic syndromes [see comments]. Eur J Haematol 1992; 49(5): 234-8 |
| Study 18 | Salo M and Simell O; Hemiarginate Therapy for Porphyria Crisis of Tyrosinemia; Annual Meeting of the European Society for Pediatric Research, Sept. 1-4 1991, Zurich, Switzerland. |
| Study 19 | Dover S B, Graham A, Fitzsimons E*, et al.*; Haem-arginate plus tin-protoporphyrin for acute hepatic porphyria [letter]. The Lancet 1991; 338(8761): 26 |
| Study 20 | Manning D J and Gray T A; Haem arginate in acute hereditary coproporphyria. Arch Dis Childhood 1991; 66(6): 730-1 |
| Study 21 | Mustajoki P, Himberg J J, Tokola O*, et al.*; Rapid normalization of antipyrine oxidation by heme in variegate porphyria. Clin Pharmacol Ther 1992; 51(3): 320-4 |
| Study 22 | Mustajoki P and Nordmann Y; Early administration of heme arginate for acute porphyric attacks. Arch Intern Med 1993; 153(17): 2004-8 |