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FDA Docket No. 2004N-0050

Safety and Effectiveness Information for  
Piroctone Olamine

Submitted Pursuant to 21 C.F.R. § 330.14(f)  
and § 330.10(a)(2)

August 13, 2004

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## **Introduction**

Clariant submits the following safety and effectiveness information to support the use of piroctone olamine (tradename Octopirox ®) as a single active ingredient in topical OTC products to relieve or control dandruff, seborrheic dermatitis, and/or psoriasis, consistent with the final OTC monograph for these products found at 21 C.F.R. Part 358, Subpart H (21 C.F.R. §§ 358.701- .750). The proposed concentrations are 0.05% to 0.5 % in leave-on and 0.1% to 1.0 % in rinse-off dosage forms.

Piroctone olamine was the subject of a Time and Extent Application (TEA), through which FDA found the ingredient and its proposed use eligible for consideration in the OTC drug monograph system. 69 Fed. Reg. 7652 (February 18, 2004). The deadline for the submission of safety and effectiveness data was extended to August 16, 2004. 69 Fed. Reg. 28932 (May 19, 2004).

**I. Labels and all labeling (preferably mounted and filed with the other data-facsimile labeling is acceptable in lieu of actual container labeling)**

Pursuant to 21 C.F.R. § 330.14 (f) (1), this information is not required.

**II. A statement setting forth the quantities of active ingredients of the drug**

Pursuant to 21 C.F.R. § 330.14 (f) (1), this information is not required.

### **III. Animal Safety Data**

#### **A: Individual Active Components**

##### **1 Controlled Studies**

###### **1.1 Acute toxicity**

###### **1.1.1 Acute oral toxicity**

###### **1.1.1.1 Acute oral toxicity in female SPF-Wistar rat**

The acute oral toxicity of Octopirox was investigated in rats using suspensions in sesame oil at a concentration of 25 %. 10 female SPF-Wistar rats each were administered Octopirox by single-dose gavage at dose levels of 4000 / 6300 / 7100 / 8000 / 9000 / 10000 or 15000 mg/kg body weight. After application the animals showed the following symptoms: Disequilibrium, dyspnoe and convulsions. The LD50 was calculated to be 8100 mg/kg body weight.

Reference: Acute oral toxicity of H72 6146 A (Octopirox in female SPF-Wistar rats, Study-No. 74.0229, Hoechst AG. submission-No.: R1

###### **1.1.1.2 Acute oral toxicity in male and female beagle-dogs**

The acute oral toxicity of Octopirox was investigated in beagle-dogs using suspensions in sesame oil at concentrations of 3.125 % (only for the lowest dose) or 25 %. One male and one female beagle-dog per group received 125 / 500 / 1000 / 2000 or 4000 mg/kg body weight by stomach tube and were observed for 14 days. After application vomiting of the animals could be observed at all dose-levels except the lowest tested. No additional side-effects on health and no deaths occurred. Thus the LD50 of Octopirox after oral administration to beagle-dogs is greater than 4000 mg/kg body weight.

Reference: Acute oral toxicity of H 72 6146 A (Octopirox) in male and female beagle-dogs; Study No. 74.0205, Hoechst AG. Submission-No.: R2

###### **1.1.2 Acute dermal toxicity**

###### **1.1.2.2 Acute dermal toxicity in female SPF-Wistar-rats**

The acute dermal toxicity of Octopirox was investigated in rats using undiluted but pasted material (1.0 g Octopirox + 0.8 ml of 0.9 % NaCl solution). The pH-value of the test preparation was 9.8. A dosage of 2000 mg Octopirox per kg body weight was applied onto the

shorn, intact dorsal skin of 5 male and 5 female SPF-Wistar rats. Following a dermal exposure of 24 hours, the occlusive dressing was removed and the treated skin area was washed to remove unabsorbed portions of the test compound. The following observation period lasted 14 and 21 days for males and females, respectively. Throughout the study no deaths occurred. After removal of the occlusive dressing the animals exhibited less spontaneous activity, and the gait of individual females was unsteady. However, these symptoms were no longer observed from the second day after application. Furthermore, there were marked irritation reactions and erosions in the treated skin area. No other macroscopic changes were detected on dissection of the animals killed at the end of the study. Since no deaths occurred, the median lethal dose (LD50) of Octopirox after dermal administration is greater 2000 mg/kg body weight in male and female rats.

Reference: Acute dermal toxicity of Octopirox® in male and female Wistar rats; Study-No. 86.1448, Hoechst AG. Submission-No.: R3

### **1.1.3 Acute inhalation toxicity**

#### **1.1.3.1 Acute inhalation toxicity in SPF-Sprague-Dawley rats**

Three groups of 5 male and 5 female Sprague-Dawley rats were exposed to a dust aerosol atmosphere of Octopirox at actual concentrations of 4.4 / 4.9 or 2.0 mg/l. The equivalent aerodynamic diameters of the test material aerosols were 10 microns for the 4.4 mg/l exposure group, 4.4 microns for the 4.9 mg/l exposure group and 4.2 microns for the 2.0 mg/l exposure group. One male and three females from the 4.9 mg/l group died either during the exposure or within 24 hours post-exposure. A high incidence of labored breathing and gasping was noted in the two groups exposed to the smaller particle size. Body weight gain was depressed except for females exposed to 2.0 mg/l. Macroscopic abnormalities observed at necropsy, white material in the trachea, gas filled intestines, red mottled lungs and dark kidneys, were only observed in those animals which died on study. No exposure related abnormalities were noted in those animals surviving 14 days. Based on this study the LC50 was estimated to be equal-to-or-greater-than 4.9 mg/l.

Reference: OECD Acute Inhalation Toxicity Evaluation of Octopirox; Study No. 191-1456, International Research and Development Corporation, 21.2.1990. Submission-No. R54

### **1.1.4 Acute irritation/Corrosion studies**

#### **1.1.4.1 Acute dermal irritation in the rabbit (pure product)**

Octopirox was tested for acute dermal irritation / corrosion properties in rabbits using pure material. Three rabbits were treated with 500 mg Octopirox (moistened with 0.4 ml isotonic saline; pH = 9.8). Following a dermal exposure period of 4 hours, the semi-occlusive dressing was removed and all remnants of the test substance were carefully removed from the skin using warm tap water. One hour up to 72 hours after removal of the patches the treated skin exhibited very slight to moderately severe erythema. Seven days after application all signs of irritation were reversible. Based on these results, pure Octopirox must be considered as an irritant to the skin.

Reference: Octopirox® -Test for primary dermal irritation in the rabbit; Study-No. 86.1390, Hoechst AG, Submission-No.: R4

#### **1.1.4.2 Acute dermal irritation in the rabbit (test concentration in range of application)**

Several studies were performed to evaluate primary skin irritation of Octopirox using test-concentrations in the range of application. For this purpose different formulations and shampoo preparations containing 0 / 0.5 or 1.0 % Octopirox were tested. 0.5 ml of the respective test-preparations were applied to the intact and scarified skin of 6 rabbits. Following a dermal exposure period of 24 h, the occlusive dressing was removed and all remnants of the test-preparations were carefully rinsed from the skin. All preparations tested either with or without Octopirox were found to be slightly irritant. Therefore it can be concluded, that Octopirox-formulations common in use have a sufficient local tolerance.

References:

Primary skin irritation of a preparation of 0.5 % Octopirox, 12.5 % Steinapol SBFA 30 (40 %), 0.11 % citric acid and 86.89 % water (pH 7.0) in rabbits (patch test); Report No. 79.0735, Hoechst AG. Submission-No.: R5.

Primary skin irritation of a preparation of 1 % Octopirox, 0.33 % citric acid, 75 % PEG 400 and 23.67 % water (pH 7.0) in rabbits (patch test); Report-No. 79.0736, Hoechst AG. submission-No.: R6.

Skin tolerance of a preparation of 1.0 % Octopirox (Op. E001), 0.3 % citric acid and 98.7 % 1,2-propylene glycol (pH 7.0) in rabbits; Report-No. 79.0737, Hoechst AG. submission-No.: R7.

Primary skin irritation of a preparation of 0.5 % Octopirox, 12.5 % Steinapol SBFA 30 (40 %), 0.11 % citric acid and 86.89 % water (pH 7.0) in New Zealand rabbits (patch test); Report-No. 79.0763, Hoechst AG. Submission-No.: R8.

Primary skin irritation of 1 % Octopirox, 0.33 % citric acid, 75 % PEG 400 and 23.67 % water (pH 7.0) in New Zealand rabbits (patch-test); Report-No.: 79.0764, Hoechst AG. Submission-No. R9.

Skin tolerance of a preparation of 1 % Octopirox (Op. E 001), 0.3 % citric acid and 98.7 % 1,2-propylene glycol (pH 7.0) in New Zealand rabbits; Report-No. 79.0765, Hoechst AG. submission-No.: R10.

#### **1.1.4.3 Acute eye irritation in the rabbit**

Several studies were performed to evaluate primary eye irritation of Octopirox using different shampoo preparations containing 0 / 0.3 and 0.5 % Octopirox. 0.1 ml of the respective solution was applied into the left conjunctival sac of 6 rabbits. The right eye served as a control. Assessments were made 1, 7, 24, 48 and 72 hours after treatment. After the 24 hour reading, all treated eyes were rinsed with physiological saline. All shampoo preparations tested either with or without Octopirox were found to be slightly to moderately irritant.

References:

Study of eye irritation of MA REF 0370 (Shampoo with 0.3 % Octopirox) in rabbits; Report-Nr. 77.1090, Hoechst AG. submission-No.: R11

Study of eye irritation of MA REF 03701 (Shampoo without Octopirox) in rabbits; Report-No. 77.1126, Hoechst AG, Submission-No: R12.

Study of eye irritation of MA REF 0380 (Shampoo with 0.3 Octopirox) in rabbits; Report-No. 77.1092, Hoechst AG. Submission-No.: R13.

Study of eye irritation of MA REF 03801 (Shampoo without Octopirox) in rabbits; Report-No. 77.1128, Hoechst AG. Submission-No.: R14

Study of eye irritation of HS REF 03790 (Shampoo with 0.5 % Octopirox) in rabbits; Report-No. 77.1127, Hoechst AG. Submission-No.: R15

Study of eye irritation of HS REF 037901 (Shampoo without Octopirox) in rabbits; Report-No. 77.1129, Hoechst AG. Submission-No.: R16

#### **1.1.4.4 Acute eye irritation in the rabbit**

Primary eye irritation was investigated in rabbits using preparations of 0.2 % Octopirox in 50 % Isopropanol in water and with 50 % aqueous Isopropanol without Octopirox. 0.1 ml of the respective test-solution, adjusted to a pH of 7.0 with citric acid, were installed into the left conjunctival sac of 6 rabbits. The right eye was left untreated in all cases and served as a control. Assessments were made 1, 7, 24, 48 and 72 hours after application. According to the

results of these studies, the test-preparations with and without Octopirox must be considered as slightly irritant.

References:

Study of eye irritation of Octopirox in aqueous Isopropanol in rabbits; Report-No. 79.0026, Hoechst AG. Submission-No.: R17.

Study of eye irritation of aqueous Isopropanol in rabbits; Report-No. 79.0027, Hoechst AG. Submission-No.: R18.

### **1.1.5 Sensitization studies**

#### **1.1.5.1 Testing for sensitizing properties in the guinea pig using the Buehler-test**

Possible sensitizing properties of Octopirox were evaluated in Pirbright White guinea pigs using the method of Buehler. Since test concentrations of 40 % were tolerated by the guinea pigs without signs of irritation and higher concentrations were too viscous for application, induction exposure and challenge treatment were performed with the 40 % concentration of the test-substance. For induction exposure 0.5 ml of the 40 % dilution was percutaneously applied 9 times in 3 weeks to the intact dorsal skin of 10 male Pirbright White guinea pigs in a occlusive patch test.

Exposure was 6 hours on the days of treatment. After the last application, the animals remained untreated for 14 days. Subsequent to this recovery phase challenge treatment was carried out by application of 0.5 ml of the 40 % dilution under an occlusive patch for 6 hours. During the induction phase marked signs of irritation occurred which, however, were completely reversible within the recovery period. Challenge treatment with 0.5 ml of the 40 % dilution caused no signs of irritation in any guinea pig. In addition, the 5 non-sensitized control animals also showed no dermal reactions following challenge treatment. Thus, testing for dermal sensitization with Octopirox in the guinea pig caused no hypersensitive reactions.

Reference: Testing for sensitizing properties of the substance H72 6146 A (Octopirox) in the guinea pig (by the method of E. V. Buehler); Report-No. 76.0027, Hoechst AG; Submission-No.: R19

#### **1.1.5.2 Testing for sensitizing properties in the guinea pig**

Octopirox was examined for its capacity to cause contact allergy by the maximization test according to Magnusson and Kligman with guinea pigs. Two groups each consisting of 10 animals were used. One group was sensitized and challenged with Octopirox. The second was sensitized with the vehicle alone and challenged with Octopirox. Similarly, 2 groups of 5

animals each were treated with 2,4-dinitrochlorbenzene as positive control. Induction exposure included one intracutaneous injection of 0.1 ml of a 0.05 % solution of Octopirox in propylene glycol emulsified in Freund's complete adjuvant (1:1). One week after this first sensitization, a second induction was carried out by covering the injection sites with 0.4 ml of a 5 % solution of Octopirox in propylene glycol. The patch was fixed by occlusive dressing and held for 48 hours. Challenge was made 14 days after the end of the second sensitization using 0.05 or 0.1 % solutions of Octopirox. The animals sensitized and challenged with Octopirox showed skin reactions similar in degree to those in the control group sensitized with the vehicle propylene glycol and challenged with octopirox.

In the positive control group, the noted changes were markedly more severe in all the test animals. In conclusion, Octopirox is considered to have no sensitizing potential.

Reference: Maximization test of Piroctone Olamine in the guinea pig; Report of S. Tanaka, H. Morioka, M. Miyamoto and T. Sakaguchi, Hoechst Japan Ltd., Department of Biological Science, May 31, 1983. Submission-No.: R20

#### **1.1.5.4 Photocontact allergy test in the guinea pig**

Possible photocontact sensitivity of Octopirox was investigated in guinea pigs using the method of Morikawa. For induction a 5 % solution of Octopirox in propylene glycol was applied to the shaved skin of 10 guinea pigs. Applications were performed 5 days a week for 2 weeks. 30 minutes after each administration, the treated skin was irradiated for 2 hours using UV-light.

Two weeks after the last induction treatment challenge exposure was performed using test-solutions containing 0.03 / 0.1 or 0.3 % Octopirox in propylene glycol. The test-solutions were applied symmetrically onto the left and right side of the back skin and one side then was irradiated for 2 hours using UV-light.

The photosensitivity was evaluated 24, 48 and 72 hours after the end of irradiation by observing the skin reaction at the area where the test material was applied and comparing the sites of irradiation and non-irradiation. Following induction and challenge exposure with Octopirox, no skin reactions were observed in any of the animals at both irradiated and non-irradiated sites. Thus, Octopirox is considered to have no photocontact sensitivity.

Reference: Photocontact allergy test of the Piroctone Olamine; Tamaka, S.; Morioka H.; Myamoto, M.; Sakaguch T.; Hoechst Japan Ltd. Department of Biological Science, June 1, 1983. Submission No., R22

## **1.2 Subacute toxicity**

### **1.2.1 Oral application**

#### **1.2.1.1 Repeated-dose (30 days) oral toxicity in rats**

In a 30 day study Octopirox was administered daily to groups of 10 male and 10 female SPF-Wistar rats via gastric-tube at dose levels of 0 / 4 / 15 / 55 / 210 or 800 mg/kg body weight. Except one male and one female of the highest dose-group all animals survived the treatment. An increase of relative food consumption was noticed in the male animals of the 210 mg/kg dose-group and in the females of the 800 mg/kg dose group. In addition retardation of body weight gain could be observed in the male animals of the 800 mg/kg dose-group. The haematological investigation revealed a decrease of erythrocyte-values, haemoglobin, haematocrit and an increase in reticulocytes and thrombocytes in males and females of the highest dose-group. The clinical chemistry and urinalyses did not show any treatment related abnormalities. Gross examination of the organs revealed no macroscopically visible changes. Although signs of a partial damage of kidney tubulli could be observed in the two intercurrent deceased animals and in one animal of the highest dose-group, these changes were not considered to be treatment-related since these findings were not seen in a subchronic, 90 day study in rats. Based on the results obtained, the no toxic effect level was placed at 55 mg/kg body weight and 210 mg/kg body weight for male and female animals respectively.

Reference: Oral range-finding study (30 days) of Octopirox in SPF-Wistar-rats; Report-No. 76.0450, Hoechst AG, submission-No.: R24

#### **1.2.1.2 Repeated-dose (30 days) oral toxicity in beagle dogs**

Octopirox was investigated for possible systemic effects in a 30 day study using groups of 2 male and 2 female beagle dogs. They were administered the test compound daily at dose-levels of 0 / 16 / 40 and 100 mg/kg body weight via the diet. During the experiment no deaths occurred and no abnormalities in behaviour were observed. Food and water consumption as well as body weight gain were not affected and corresponded to that of the controls. Haematological investigations, clinical chemistry and urinalysis did not reveal adverse effects. The results of the electrocardiographic and ophthalmological investigations were normal. Gross examination as well as histopathological investigations of organs did not show any morphological differences between treated and control animals. Because there was no sign of substance related toxicity throughout the study the no toxic effect level of Octopirox after repeated administration to beagle dogs is greater than 100 mg/kg body weight.

Reference: A repeated-dose (30 days) oral toxicity study of Octopirox in beagle dogs; Report-No. 76.0400, Hoechst AG. Submission-No.: R25

## **1.2.2 Dermal application**

### **1.2.2.1 Repeated dose (5 weeks) dermal toxicity in rats**

Octopirox was administered to groups of 15 male and 15 female Spraque-Dawley rats by subcutaneous injection at dose levels of 0 / 100 / 500 or 2000 mg/kg body weight. The animals were treated once daily for a period of 5 weeks. Following the treatment, surviving animals were subjected to a 2 week recovery experiment. One male of the 500 mg/kg group and two males of the 2000 mg/kg dose-group died during the treatment-period. Neither abnormalities in general symptoms nor deaths were observed in the 100 mg/kg dose-group. Changes in general health condition were noticed in the 500 mg/kg and 2000 mg/kg dose-group and included loss of hair gloss, hard hairs, piloerection and depressed body weight gain in both males and females. Haematological findings included anemia, low lymphocyte count and high segmented neutrophil count in both sexes of the 500 mg/kg and 2000 mg/kg dose-group. In addition, high leucocyte count in females of the medium and high dose groups could be noticed. Serum biochemistry revealed low total protein and high urea nitrogen values in the 500 mg/kg dose-group and, only in females of this group, high cholesterol values. Changes in the 2000 mg/kg dose-group included low values of total protein and in the albumine:globulin ratio as well as elevations of urea-nitrogen, cholesterol and alkaline phosphatase values. Urinalysis indicated increased values of Na<sup>+</sup> in both sexes of the 500 mg/kg and 2000 mg/kg dose-group. The ophthalmologic examinations revealed no abnormalities in any of the treatment groups. Although changes in absolute and relative organ weights were observed in both sexes of the 500 mg/kg and 2000 mg/kg dose-group, no histopathological abnormalities were detected. At necropsy, the residue of the test compound was found at the dorsal injection sites of all dosage groups. In addition, marked inflammatory changes at the injection sites were seen at the gross and histopathological examinations of the 500 mg/kg and 2000 mg/kg body weight treated animals. During the recovery period, indications of a reversible nature of the mentioned changes were found. Especially those in general symptoms, body weight, haematology and organ weights showed favorable recoveries.

Reference: Five weeks subcutaneous toxicity of Piroctone Olamine in rats; Report of S. Toyoshima (Kejo Gijuku University, Department of medial Science), H. Sato (Sasaki Research Institue), R. Sato, H. Sato and M. Motoyama (Japan Experimental Medical Research Institute Co., Ltd.), august 18, 1981. Submission-No.: R26.

#### **1.2.2.2 Subacute dermal toxicity studies with shampoo and hair-lotion formulation in rabbits**

Dermal toxicity studies were performed using different types of Octopirox preparations. Groups of 5 male and 5 female rabbits were topically administered one shampoo-formulation containing 0.5 % of Octopirox and, in a second experiment, one hair-lotion containing 0.1 % Octopirox. 100 mg of the shampoo-preparation was applied once daily except sundays (30 applications in 36 days). 5 minutes after each application, the treated skin was rinsed with water. No mortality occurred during this study. Behaviour and general condition as well as food consumption and body weight gain were not affected by the treatment. Heamatological, clinical-chemistry and urinalyses did not reveal any abnormalities. Gross examination as well as histopathological investigation of the organs did not show any morphological differences between treated and control animals. In a second experiment, 0.1 ml of the hair-lotion was applied 3 to 4 times a week onto the shaved, intact skin of 5 male and 5 female rabbits (30 applications in 64 days). Except one female rabbit, which died during this study, all other animals survived. Although the cause of the death could not be found, it was not considered to be a substance related effect. General condition, food consumption and body weight development of the animals, including the intercurrent deceased animal, as well as haematology, clinical-chemistry and urinalyses were not modified by the treatment. In addition, also the macroscopic and microscopic examinations of the organs did not show any treatment related abnormalities.

Reference: Subacute dermal toxicity study in male and female rabbits with a hair-lotion and shampoo-preparation containing H 72 6146 A (Octopirox); Report-No. 76.0294, Hoechst AG. submission-No.: R27

### **1.3 Subchronic toxicity**

#### **1.3.1 Oral application**

##### **1.3.1.1 Repeated-dose (90 day) oral toxicity study in rats**

Octopirox was investigated for possible systemic effects in a 90 day study using groups of 25 male and 25 female SPF-Wistar-rats. They were administered the test substance once daily via gastric tube 5 days per week at dose-levels of 0 / 40 / 100 or 250 mg/kg body weight.

After the treatment period of 90 days, 15 male and 15 female animals of each group were killed and subjected to histopathological examinations. The remaining animals served as recovery groups for another 14 days. A total of seven rats died intercurrently. However, since no histopathological abnormalities could be detected in these animals, the cause of death was not considered to be a substance related effect. General behaviour of the animals was not influenced by the treatment. Body weight gain in the male animals of the highest dose-group was decreased compared to the controls and relative food consumption was increased in both males and females of the highest dose group. These changes tended to be reversible as could be seen in the recovery group. Except a slight decrease of haemoglobin, haematology revealed no treatment-related effects attributable to the treatment. In addition, gross examination as well as histopathological investigation did not show morphological differences in any organ between test and control animals. Based on the results of this study, the no toxic effect level was placed at 100 mg/kg body weight.

Reference: Repeated-dose (90 days) oral toxicity study of Octopirox in rats; Report-No. 77.0752, Hoechst AG. Submission No.: R28

#### **1.3.1.2 Repeated-dose (90 days) oral toxicity in beagle dogs**

Octopirox was investigated for possible systemic effects in a subchronic toxicity study with beagle dogs. Groups of 4 male and 4 female dogs received Octopirox at daily dose-levels of 0 / 16 / 40 or 100 mg/kg body weight with the diet for 90 consecutive days. Behaviour, general condition and food consumption as well as body weight gain were not affected by the test compound. The results of the ophthalmologic examination revealed no abnormalities. Haematology, clinical-chemistry and urinalysis showed no treatment related adverse effects. Gross examination as well as histopathological investigation of the organs did not show any morphological changes. On the basis of the results obtained, the no toxic effect level of Octopirox after oral application to beagle dogs is greater than 100 mg/kg body weight.

Reference: Repeated-dose (90 days) oral toxicity study of Octopirox in beagle dogs, Report No. 77.0215, Hoechst AG. Submission-No.: R29

### **1.4 Chronic toxicity**

#### **1.4.1 Six month percutaneous toxicity study in rats**

Octopirox was investigated for possible systemic effects in long-term toxicity studies using the dermal exposure route. Test solutions containing 0 / 0.5 or 1 % Octopirox in propylene glycol were painted onto the shaved back skin of 16 male and 16 female rats per group. A

fourth group was treated with distilled water as control. 0.2 ml of these solutions were applied once daily, 6 days per week for 6 consecutive months. Following this 6 month regimen of topical application of the test article solutions, 4 male and 4 female animals of each group were observed for additional 7 weeks. Scratch-wounds were observed at the sites of topical application of the test solutions as well as after application of propylene glycol alone. However, no sign of irritation of the skin (redness, oedema) were noticed. In addition, no abnormalities in terms of general symptoms and no deaths in any of the test groups occurred. Regarding body weight, a depression of body weight gain was recorded for male animals treated with 1 % Octopirox and for the females of the propylene glycol group. However this was not considered to be a systemic effect of Octopirox. The ophthalmologic examinations revealed no abnormalities. Haematology, clinical-chemistry and urinalysis have not shown any adverse effects. Gross examination and histopathology of the organs showed no changes attributable to the treatment. Histopathological studies of the skin revealed slight thickening of the epithelium at the site of application of the test articles. Since no changes in the skin were detected in the histopathological studies conducted at the end of the 7-week recovery study, no toxicological significance is attached to this point. In conclusion, mixing of Octopirox into external-use products such as shampoo and hair-lotions up to a concentration of 1 % does not represent a toxicological risk in terms of safety.

Reference: 6 month chronic percutaneous toxicity of Piroctone Olamine on rats; Report No. T-368-1 of R. Itoe and S. Kajawara, February 15, 1983. Submission No.: R30

#### **1.4.2 12 month percutaneous toxicity study in rats**

Test solutions containing 0 / 0.5 or 1 % Octopirox in propylene glycol were painted onto the shaved back skin of 14 male and 14 female rats per group. A fourth group was treated with distilled water as control. 0.2 ml of these solutions were applied once daily, 6 days per week for 12 consecutive months. Following this treatment 4 male and 4 female animals of each group were observed for additional 7 weeks. Immediately after the beginning of the topical application of the test article solutions, pityriasis-like changes and slight scratch-wounds were observed at the treatment sites of male and female rats of each test-group excluding the control groups. These macroscopically visible changes disappeared within 2 weeks after termination of the study, as could be seen in the recovery group. Regarding mortality, one male treated with propylene glycol alone died, while 2 male rats in the 0.5 % group and one male in the 1.0 % group died. Autopsy and histopathological studies on those animals revealed slight changes in the liver, kidney, and lung which were not considered to be

substance-related. In general, no sticking changes were observed in relation to behaviour, food consumption and body weight gain. Ophthalmologic investigations showed no abnormalities. Haematology, clinical-chemistry as well as unrinalysis revealed no changes attributable to the treatment. Gross examination and histopathology of the organs also revealed no abnormalities. Thus it is concluded, that Octopirox in concentrations of up to 1 % in external-use products represented no risk in terms of safety even if such products were applied chronically.

Reference: One year chronic percutaneous toxicity of Piroctone Olamine in rats, Report No. T-368-2 of R. Itoh and S. Kajawara, September 20, 1983. submission.: R 31

## **1.5 Genotoxicity**

### **1.5.1 In vitro studies**

For assessing possible mutagenic effects of Octopirox several short-term mutagenicity tests were conducted. Using the procedure of the so called Ames-Test the following tests were performed:

#### **1.5.1.1 Ames Test**

Octopirox was investigated for mutagenicity with the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537. The tests were performed in the presence and in the absence of a metabolizing system derived from rat liver homogenate (S9-Mix). A dose-range of 0.2 to 500 µg/plate was used. Based on the results obtained, Octopirox is not mutagenic in these bacterial test systems either with or without exogenous metabolic activation.

Reference: Octopirox: Test for mutagenicity in bacteria strains in the absence and presence of a liver preparation, Report No. 77.0815, Hoechst AG. submission-No.: R32

#### **1.5.1.2 Ames-Test**

Octopirox was investigated for mutagenicity using the Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538. A dose-range of 1 to 200 µg/plate was used and tests were carried out in the presence and in the absence of an exogenous metabolizing system (S9-mix). At the highest concentrations used, Octopirox inhibited bacterial growth. At lower concentrations however, Octopirox treatment showed no abnormal increase in the number of revertant colonies of any strain tested. From this results, Octopirox is considered to be not mutagenic in this test system.

Reference: Mutagenicity test of Piroctone Olamine; O. Nahanishi, H. Morioha, M. Miyamoto, Hoechst Japan Ltd., Department of Biological Science, April 27, 1982. Submission-No.: R33

### **1.5.1.3 Ames Test**

Octopirox was tested for mutagenicity in two independent experiments using different charges of the test-compound. Salmonella typhimurium strains TA98, TA100 and TA1538 were used. Investigations were carried out in a dose-range of 5 to 250 µg/plate only with metabolic activation (S9-mix). The test compound proved to be very toxic to the bacteria at 50 up to 250 µg/plate. From the results obtained, it can be stated that Octopirox is not mutagenic but cytotoxic in these bacterial test systems using exogenous metabolic activation.

References:

Study of mutagenic potential of the compound Octopirox Charge W 020 in strains of Salmonella typhimurium (Ames-Test); Report-No. 82.0692, Hoechst AG. Submission-No.: R34

Study of the mutagenic potential of the compound Octopirox OP. A 038 in strains of Salmonella typhimurium (Ames-Test); Report-No. 82.0693, Hoechst AG. Submission-No.: R35.

## **1.5.2 In vivo studies**

### **1.5.2.1 Micronucleus-test in NMR-mice**

Octopirox was investigated for possible mutagenic effects in the micronucleus-test. Groups of 10 male and 10 female NMRI-mice were administered the test compound orally by gavage at dose levels of 0 / 125 / 250 or 500 mg/kg body weight. The animals were treated twice in an interval of 24 hours and sacrificed 6 hours after the last application. The incidence of micronucleated polychromatic erythrocytes was not increased in comparison with the controls. The number of normochromatic erythrocytes containing micronuclei was also not increased. The ratio of polychromatic / normochromatic erythrocytes in both male and female animals remained unaffected by the treatment. On the basis of the results obtained, Octopirox was not mutagenic in the micronucleus-test.

Reference: An oral mutagenicity study (Micronucleus-test) with Octopirox in mice; Report-no. 77.0677, Hoechst AG. Submission-No.: R 36

#### **1.5.2.2 Micronucleus-test in IRC-mice**

Single and repeated (4 days) administration of Octopirox suspended in 2 % Arabian rubber solution was given intraperitoneally to groups of male IRC-mice. For the single administration, dose levels of 0 / 31.3 / 62.5 or 125 mg/kg body weight were used. For the 4 day repeated administration four equal portions of 0 / 15.6 / 31.3 / 62.5 or 125 mg/kg body weight were given daily for four days. The animals were sacrificed 2 hours after the treatment and the incidence of micronucleated cells was investigated. As a result, there was no significant increase in the formation of micronuclei in the mouse polychromatic erythrocytes either in the single or the 4 day repeated administration of Octopirox as compared to the controls.

Reference: Micronucleus-test of Piroctone Olamine in mice; M. Harusaka, K. Nabeshima; Biological Science Laboratories, Lion Corporation, 1981. Submission-No.: R 37

#### **1.5.2.3 Cytogenetic assay**

Octopirox was investigated for mutagenic activity in Chinese hamster bone marrow cells by measuring the induction of chromosome aberrations after *in vivo* treatment of the animals. 15 male and 15 female Chinese hamsters were administered the test compound via a single intraperitoneal injection using 3500 mg/kg body weight as dose level. Triethylenemelamine was used as positive control. Groups of 5 male and 5 female animals were killed 6, 24 and 48 hours after the application. Bone marrow cells were isolated and scored for chromosomal aberrations. As a result, Octopirox did not induce chromosomal aberrations and is therefore considered negative in the aberration test in Chinese hamster bone marrow cells.

Reference: Mutagenicity evaluation of PKOD-A038 in the Chinese hamster bone marrow cytogenetic assay; Report of Litton Bionetics, Inc., March 1984. Submission-No.: R 38

#### **1.5.2.4 DNA-binding assay**

Octopirox was investigated for possible genotoxic effects in a DNA-binding study *in vivo*. 6-[<sup>14</sup>C]-Octopirox monoethanolamine salt was administered subcutaneously to 3 male rats using 35 mg/kg body weight as dose level (= 3.5 mCi/kg body weight). 48 hours after application, liver DNA was isolated. The study did not give any indication on a very low limit of detection for a genotoxic activity *in vivo* of Octopirox mediated by DNA-binding.

Reference: Lack of in vivo binding to DNA of Piroctone Olamine; P.Sagelsdorff, W.K. Lutz, Ch. Schlatter; Swiss Federal Institute of Technology and University of Zürich, Sept. 16, 1983. Submission No.: R 39

## **1.6 Reproduction effects**

### **1.6.1 Embryotoxicity study in rabbits**

Possible effects of Octopirox on embryonic and fetal development were investigated using groups of 15 pregnant female rabbits. They were administered Octopirox orally by gavage once daily on days 7 – 19 of gestation at dose levels of 0 / 16 / 32 or 63 mg/kg body weight. On day 29 of pregnancy the dams were killed and delivered. The examinations demonstrated that repeated administration of Octopirox in the sensitive phase of organogenesis caused no impairment of general health status of the dams and no disturbance of intrauterine development of the fetuses. The examinations of the fetuses for developmental status, externally ascertainable abnormalities, visceral and skeletal abnormalities, and a 24-hour viability suggested no embryotoxic and teratogenic action of Octopirox.

Reference: An oral embryotoxicity study with Octopirox in rabbits; Report-No.: 79.0603, Hoechst AG. Submission No.: R 40

### **1.6.2 Embryotoxicity study in rats**

Octopirox was administered once daily subcutaneously to groups of pregnant female rats from day 7 to 17 of gestation at dose levels of 0 / 100 / 500 or 2000 mg/kg body weight. The numbers of the females treated were 26 in the control group, 22 at 100 mg/kg body weight, 21 at 500 mg/kg body weight and 24 at 2000 mg/kg body weight. During the administration period, depression of body weight gain and reduction in food consumption occurred in the animals of the highest dose-group. Slightly reduced food consumption also occurred in the 500 mg/kg dosage-group. Regarding maternal organ weights, a decrease in the thymus weight and increases in the spleen and adrenal weights in the 2000 and 500 mg/kg dosage-groups as well as slight increases in the liver, kidney and urinary bladder weights of the 2000 mg/kg dosage-group were observed. A decrease in the number of living fetuses and in the body weight of the living fetuses of either sex was noted in the highest dose-group. No differences occurred between any treated group and the control group in frequencies of fetuses with external, visceral, or skeletal abnormalities.

Reference: Teratological study of Piroctone Olamine in rats; S Toyoshima (Keio University), R. Satch, M. Kashima, M. Takahashi (Japan Experimental Medical Research Institute), June 30, 1981. Submission-No.: R 41

### **1.6.3. Embryotoxicity study in rats**

Octopirox was administered subcutaneously to groups of 20 pregnant rats at a dose-level of 2000 mg/kg body weight during days 6 to 20, days 7 to 17 or days 9 to 17 of gestation. The fetuses were delivered by cesarean section on day 21 of gestation. The body weight gain of the treated females was depressed in the late stage of gestation, but no death occurred in any group. There were no significant differences in the following fetal parameters between any treatment group and the control group: numbers of implantations, resorptions, dead and living fetuses, and sex ratio of the living fetuses. The body weights of the living fetuses in the treated groups were lower than the control value. As to the skeletal findings, the ossification was slightly delayed in the treated groups when compared with that in the control. Detected visceral and skeletal abnormalities were within the spontaneous range.

Reference: Teratological study of Piroctone Olamine in rats – Subcutaneously administration at different times during organogenesis; T. Kitatani, M. Akaike, K. Takayama, M. Miyamoto; Research and Development Laboratories, Hoechst Japan Ltd., April 19, 1982. Submission-No.: R 42

### **1.6.4. Segment I study in rats**

Octopirox was subcutaneously given to groups of 24 male and 24 female rats at daily doses of 0 / 20 / 50 / 100 or 500 mg/kg body weight. Males were administered the test compound for 9 weeks before mating and through the mating period, while the females were treated for 2 weeks before mating up to day 6 of gestation. Cesarean sections were performed on all pregnant females from each group on day 18 of gestation. In the highest dose-group 8 males died probably due to remarkable inflammatory changes at the application side. Additionally body weight gain was depressed in both male and female animals of this treatment group. Copulation was delayed in the 500 mg/kg dosage-group. However, the females and survived males at this dose-level were shown to have reproductive ability. At each treatment level, fetuses exhibited no changes in any parameters examined at cesarian section. No differences occurred between treated and control animals in the incidences of visceral anomalies, skeletal anomalies and variations, and delayed ossification.

Reference: Subcutaneous administration of Piroctone Olamine to rats from pre-conceptional period through early stage of gestation. R. Sto, M. Kajima, Nippon Experimental Medical Research Institute, March 22, 1983. Submission-No.: R 43

#### **1.6.5 Segment III study in rats**

Octopirox was subcutaneously administered to rats at daily doses of 0 / 20 / 100 or 500 mg/kg body weight during the last third of gestation and the period of lactation (from day 17 of gestation until day 21 after delivery). Body weight gain of the dams of the highest dose-group was slightly depressed, and body weights of all treated females were decreased during pregnancy. No effects on body weights were observed during lactation. Food consumption decreased in each treatment-group at the end of pregnancy, but no change was observed during lactation. No changes attributable to treatment occurred in the weights of organs examined. Regarding the offspring, no treatment related abnormalities were noticed in the following: various parameters examined at birth, general differentiation, functions, open field behaviour and learning ability. No changes attributable to the treatment were observed in the skeletons. Examinations of the F1 offspring for their fertility revealed no abnormalities. Various maternal (F1) and fetal (F2) parameters examined at cesarean section were unaffected.

Reference: Effects of Piroctone Olamine subcutaneously given during the last third of gestation and the period of lactation in the rat; R. Sato, M. Kajma, Nippon Experimental Medical Research Institute; March 22, 1983. Submission-No.: R 44

#### **1.6.6 Effects on reproduction of male and female rats by oral administration**

The effect of Octopirox on reproductive performance, fertility, parturition, and neonatal viability and growth was investigated using the oral exposure route. This dosing procedure was chosen to exaggerate systemic availability of the test compound compared to the relevant dermal exposure route of Octopirox in humans. Octopirox was administered via gavage to three groups of 35 male rats each beginning 64 days prior to mating and to three groups of 35 female rats each beginning 14 days prior to mating. Single daily doses of 0, 10, 100 and 250 mg/kg body weight in a combination of methylcellulose and polyethylene glycol 400 as vehicel were administered. Systemic effects were seen at the mid- and high-dose levels, but only among the male rats. These effects were slightly decreased body weight gains and slightly decreased liver weights. Heamatological findings representative of anemia occurred at the high-dose group. Offspring growth was somewhat decreased in the 250 mg/kg body

weight group whereas mating ability and reproductive performance were not affected at any dose level. Neonatal growth was not affected at 100 mg/kg body weight or less, and the NOEL with respect to reproductive parameters, including fertility, was 250 mg/kg body weight per day.

Reference: The effect of Piroctone Olamine on reproduction of male and female rats; Allgood, G.S. et al., *Fundamental and Applied Toxicology* 16, 31-40, 1991. Submission-No. R49

### **1.6.7 Effects of dietary iron supplementation on the toxicity of Piroctone Olamine**

Weanling rats of both sexes were fed 300 mg/kg body weight per day of Octopirox and were supplemented with 0, 50, 100 or 200 ppm dietary iron for six weeks. The rats given Octopirox without iron supplementation gained significantly less body weight than controls, with the effect being more pronounced in the males. These animals also developed signs of a severe microcytic, hypochromic anemia. The animals supplemented with all three levels of dietary iron grew at a rate similar to controls and the 100 ppm iron supplementation restored all hematological parameters to normal in the females. In the males slight reductions in some of the parameters were still evident. The 200 ppm supplement of iron restored all parameters to values similar to controls in both sexes. These results suggest that the mechanism of the observed toxicity of Octopirox in studies with oral administration is the prevention of dietary iron absorption by the strong chelating properties of Octopirox. These results should be taken into account when discussing Octopirox related effects when alternative exposure routes, e.g. oral compared to the relevant dermal route in humans have been used.

Reference: The effects of dietary iron supplementation on the toxicity of Piroctone Olamine in the growing rat; Nolen, G.A. et al., *Drug and Chemical Toxicology* 12: 111-121, 1989; Submission-No. R50

## **1.7 Pharmacokinetic studies**

### **1.7.1 Pharmacokinetics in rats**

Pharmacokinetics of Octopirox were investigated in rats after dermal, oral and intravenous administration. A dermal dose of approx. 2 mg <sup>14</sup>C-Octopirox per animal (in a 1.5 % shampoo preparation) was applied onto fur and back skin of rats and rubbed in for one minute. Subsequently the treated site was wiped with wet cotton wool pads, and by this procedure  $43.1 \pm 7.2$  % of the dose administered was removed. During the 7 days of study, between 0.64

and 2.27 % of the administered dose was renally excreted. On the last day of study less than 0.3 % of the administered dose was recovered in excretory products. The slight absorption process still measurable may have been due to a possible reservoir formation in or on the skin, caused by an insufficient removal of the active substance from the skin after application.

After oral administration of 0.24 mg Octopirox per kg body weight, maximum blood levels of 0.006 to 0.14 µg/ml were measured between 3 and 8 hours after treatment. Half-lives around 42 minutes and 14 hours were estimated for the biphasic elimination from blood after intravenous treatment. Independent of the route of administration, more radioactivity was excreted in feces (56-79 %) than in urine (12-22 %).

After intravenous injection the administered radioactivity was, uninfluenced by adsorption, eliminated with half-lives of about 8 and 23 hours or 35 hours. Depending on the experimental group, absorption ranged around  $68 \pm 10$  % or may be considered complete ( $93 \pm 14$  %). The very low concentrations of radioactivity measured at the end of the study in organs and tissues examined, indicate complete elimination. Specific accumulations persisting for a longer period after oral and intravenous administration were not observed in autoradiographic studies either.

Reference: Pharmacokinetic studies of Octopirox-<sup>14</sup>C after dermal, oral and intravenous administration to rats. Report-No. 01-L42-0325-80, Hoechst AG, November 27, 1980. Submission-No.: R 45

### **1.7.2 Pharmacokinetic study in dogs and rats**

Dogs received Octopirox orally per stomach tube as a suspension in sesame oil at dose levels of 50 and 100 mg/kg body weight. Analysis of the test compound in blood was performed by fluorometric determination. Depending on the absorption delay, maximal blood levels were reached after 1.25 to 3.2 hours and amounted to  $22.9 \pm 3.0$  µg/ml after 50mg/kg body weight to  $33.0$  µg/ml after 100 mg/kg body weight. The elimination occurred with a half-life of  $2.7 \pm 0.7$  hours. The areas under the serum level curves were compared and proved to be dose-dependent.

Rats received Octopirox oral per stomach tube not only as monoethanolamine salt (dosage: 100 mg/kg body weight), but also as sodiumsalt (dosage: 87.2 mg/kg body weight) and as free acid (dosage: 79.9 mg/kg body weight), all three suspended in starch mucilage. In another

study rats received by the same route Octopirox as a suspension in sesame oil at a dose-level of 100 mg/kg body weight. The individual measuring values showed a considerable range of variation. Apart from the absorption delay, no difference was found among the various salts and vehicles. Maximal serum levels of  $12.3 \pm 3.0 \mu\text{g/ml}$  were reached after  $1.2 \pm 0.3$  hours. The elimination occurred in two phases with half-lives of 0.5 hour and 4.5 hours respectively. Reference: Kinetics of Octopirox after oral administration to dogs and rats. Hoechst AG, Pharma Reserach Biochemistry, March 3, 1980. Submission-No.: R 46

### 1.7.3 Skin absorption study

Radiolabelled Octopirox was administered to rats in aqueous polyethylene glycol 200 solution, by oral intubation, intraperitoneal or subcutaneous injection and its route and rate of excretion was examined by radiotracer methods. For topical treatment [ $^{14}\text{C}$ ]-Octopirox was dissolved in an anionic shampoo base and applied to rat skin.

When given by intubation or injection [ $^{14}\text{C}$ ]-Octopirox was excreted by the rat mostly in the faeces (65 – 85 % of the dose) with smaller amounts (6 – 19 %) in the urine. Most of excretion occurred within 24 hours of dosing.

Skin penetration of Octopirox at 1 % (w/v) in the shampoo without rinsing was  $65.1 \mu\text{g/cm}^2$  under occlusive and  $38.2 \mu\text{g/cm}^2$  under non-occlusive conditions. In a „rinse off“ treatment, penetration was reduced to  $3.4 \mu\text{g/cm}^2$  under occlusive and  $2.0 \mu\text{g/cm}^2$  under non-occlusive conditions. There was a dependence of skin penetration of Octopirox on duration of contact up to 10 minutes after application.

Penetration increased significantly from  $2.4 \mu\text{g/cm}^2$  after 2.5 minutes exposure to  $45 \mu\text{g/cm}^2$  after 10 minutes duration of contact. There was no further increase in penetration of Octopirox at 20 minutes application of 1 % Octopirox in the shampoo. Skin penetration and deposition of Octopirox were both proportional to Octopirox concentration between 0.1 and 1 % (w/v). Skin penetration increased from  $0.31$  to  $3.6 \mu\text{g/cm}^2$  while deposition increased from  $0.8$  to  $7.6 \mu\text{g/cm}^2$ . There was no significant difference between the penetration through clipped skin and hairy skin from an application of 1 % Octopirox for 5 minutes followed by rinsing. Blood levels after topical application ( $15.4 \text{ mg/kg}$  body weight) without rinsing and with occlusion reached  $0.32 \mu\text{g/ml}$  at 6 hours. However, when the skin was rinsed and protected with a non-occlusive patch, blood levels were reduced to a maximum of  $0.02 \text{ ug/ml}$

at 1 hour after application. Whether given by mouth, injection or application to the skin, Octopirox was excreted essentially unchanged. Based on the results, a safety factor was estimated for the consumer using a shampoo containing 1 % Octopirox to be > 10000 so that the possibility of systemic effects of Octopirox due to absorption through the skin is negligible.

Reference: Percutaneous absorption of Octopirox; W.E. Parish, Unilever Research, Environmental Safety Laboratory, August 1983 . Submission-No.: R 47

Reference: Percutaneous absorption of Octopirox ® ; Black, J.G. and Kamat, V.B., Fd Chem. Toxic. 26: 53-58, 1988; Submission-No. R51

### 1.8 Pharmacology

A wide variety of possible, pharmacologic effects of Octopirox were investigated using both in vivo and in vitro techniques. In summary, oral administration in doses of up to 1000 mg/kg body weight, did not induce behavioural changes in mice. In addition, oral application of 5 mg Octopirox per kg body weight had no effect, either on Pervitin<sup>R</sup> induced motoric activity or on Hexobarbital – induced sleeping time in mice. Oral administration of Octopirox (5 mg/kg body weight) had no inhibiting effect on pentylene-tetrazole – induced extensor convulsions in mice. Tetrabenazine induced ptosis in mice was not antagonized by treatment with 5 mg Octopirox per kg body weight. Additionally oral doses of 5 mg/kg body weight exhibited no protective effect against electroshock-induced extensor convulsions in mice. In the heat pain test in mice analgesic effects of Octopirox could not be demonstrated. Octopirox had no effect on contractions induced by carbachol, histamine or BaCl<sub>2</sub> in the isolated guinea pig ileum. In addition, Octopirox had no relaxing effect on carbachol-induced contractions of the isolated guinea pig trachea. Possible cardiovascular effects of Octopirox were investigated in anesthetized cats. Intravenous doses of 3 or 5 mg/kg body weight did not induce acute changes in all parameters measured. Octopirox also did not antagonize histamine-induced bronchoconstriction in guinea pigs, had no diuretic effect in liqued-loaded rats and had no effect on blood glucose in glucose-loaded rats. In addition, Octopirox had no anti-inflammatory effect on the carrageen-induced paw edema in rats as well as no antipyretic effect in rats. Because of the results obtained, Octopirox could be considered as pharmacologically relatively inert.

Reference: Report on general pharmacology of Octopirox; Pharma Research Pharmacology, Hoechst AG, December 10, 1976. Submission-No.: R48

**2 Partially Controlled or Uncontrolled Studies**

None

**B: Combinations of the Individual Active Components**

**1 Controlled Studies**

Clariant is not seeking authorisation to use piroctone olamine in combination with other active ingredients.

**2 Partially controlled or uncontrolled studies**

Clariant is not seeking authorisation to use piroctone olamine in combination with other active ingredients.

**C: Finished Drug Product**

**1 Controlled Studies**

Studies on finished drug products containing piroctone olamine (R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R27, R 45, R 47, R51) are included in the submission under section IIIA for sake of better consistency.

**2 Partially controlled or uncontrolled studies**

none available

## **IV. Human Safety Data**

### **A: Individual Active Components**

#### **1 Controlled Studies**

##### **1.1 Testing for sensitizing properties in humans**

Possible sensitizing properties of Octopirox were evaluated in humans using the repeated insult patch test. 0.5 % Octopirox in a Sulphosuccinic acid ester-water solution (1:1 v/v) was applied topically 18 times in 3 weeks to 50 healthy volunteers. 10 days after the last application challenge exposure was carried out using the 0.5 % Octopirox solution already described. No dermal reactions were noticed, neither during the induction phase, nor after the challenge treatment, in any of the persons tested.

Reference: Testing for sensitizing properties of the antidandruff substance H 72 6146 A (Octopirox) in humans; Report No. 75.0881, Hoechst AG, Submission No.: R21

##### **1.2 Phototoxicity in humans**

Possible phototoxic properties of Octopirox were evaluated in humans using a 0.1 % solution of Octopirox in water / isopropanol (1:1). The test solution was applied to the skin of the test persons one hour prior to ray treatment with a UV-B photo lamp. In a further study, ray treatment was performed in the UV-A range. No indications of phototoxic properties of Octopirox were noticed either in the UV-B or the UV-A range.

Reference: Phototoxicity study with Octopirox in humans; H. Tronier, Hautklinik Dortmund, 8. September 1976. Submission-No.: R23

#### **2 Partially controlled or uncontrolled studies**

not available

#### **3 Documented case reports**

No documented case reports regarding negative health effects known

#### **4 Pertinent marketing experiences that may influence a determination as to the safety of the individual active components**

The extensive marketing experience demonstrated in the time and extent application for piroctone olamine has not shown indications of adverse health effects.

**5 Pertinent medical and scientific literature**

No pertinent literature available.

**B: Combinations of the Individual Active Ingredient**

**1 Controlled studies**

Clariant is not seeking authorisation to use piroctone olamine in combination with other active ingredients.

**2 Partially controlled or uncontrolled studies**

Clariant is not seeking authorisation to use piroctone olamine in combination with other active ingredients.

**3 Documented case reports**

No documented case reports regarding negative health effects known

**4 Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components**

The extensive marketing experience demonstrated in the time and extent application for piroctone olamine and combinations with other active ingredients has not shown indications of adverse health effects.

**5 Pertinent medical and scientific literature**

No pertinent literature available.

## **C: Finished Drug Product**

### **1 Controlled studies**

#### **1.1 Patch test for investigating the skin-irritant effect of cosmetic products in humans**

A patch test to detect potential skin irritating effects or reactions indicative of contact allergy associated with piroctone olamine was conducted in human volunteers using a hair shampoo formulation representing rinse-off conditions. The surfactant formulation tested contained 0.7% (w/w) piroctone olamine. The study was conducted in the Institute for Experimental Dermatology of the University Witten-Herdecke in Germany. Study director was Prof. Dr. Hagen Tronnier. A group of 50 female and male volunteers aged between 16 and 64 took part in the study. Using a commercial test plaster, the test item was placed on the skin and left for 48 hours. After removal of the plaster the treated skin area was evaluated for positiv dermal reactions. Further assessments were made after 72 hours. As a result, no positive or dubious skin reactions were observed after either 48 or 72 hours. Based hereupon, the test formulation is considered not to be a primary skin irritant. Additionally, no indications of a sensitizing potential triggered by the ingredients of this formulation have been observed.

Reference: Patch test for investigating the skin-irritant effect of cosmetic products in humans, H. Tronnier, dated 17. June 1991; Submission No.: R52

#### **1.2 Patch test for investigating the skin-irritant effect of cosmetic products in humans**

A patch test to detect potential skin irritating effects or reactions indicative of contact allergy associated with piroctone olamine was conducted in human volunteers using a hair tonic formulation representing leave-on conditions. The surfactant formulation tested contained 0.3% (w/w) piroctone olamine. The study was conducted in the Institute for experimental dermatology of the University Witten-Herdecke in Germany. Study director was Prof. Dr. Hagen Tronnier. A group of 50 female and male volunteers aged between 16 and 64 took part in the study. Using a commercial test plaster, the test item was placed on the skin and left for 48 hours. After removal of the plaster the treated skin area was evaluated for positiv dermal reactions. Further assessments were made after 72 hours. As a result, no positive or dubious skin reactions were observed after either 48 or 72 hours. Based hereupon, the test formulation is considered not to be a primary skin irritant. Additionally, no indications of a sensitizing potential triggered by the ingredients of this formulation have been observed.

Reference: Patch test for investigating the skin-irritant effect of cosmetic products in humans, H. Tronnier, dated 17. June 1991; Submission No.: R53

**2 Partially controlled or uncontrolled studies**

none

**3 Documented case reports**

No documented case reports regarding negative health effects known.

**4 Pertinent marketing experiences that may influence a determination as to the safety of combinations of the individual active components**

The extensive marketing experience demonstrated in the time and extent application for piroctone olamine and combinations with other active ingredients has not shown indications of adverse health effects.

**5 Pertinent medical and scientific literature**

No pertinent literature available.

## **V. Efficacy data**

The studies and the scientific literature listed below reflect that piroctone olamine may be recognized as effective for the antidandruff indication. Evidence is given by studies on piroctone olamine as a single substance (stability, substantivity, anti-fungal and antibacterial spectrum) and through controlled studies and scientific literature on formulations containing piroctone olamine in products intended to be rinsed of (shampoos, hair rinses) and in products intended to be left on the scalp/hair (hair tonics). Most of these studies were either done in comparison to a placebo product or in comparison to already monographed antidandruff actives like zinc pyrithione or coal tar.

Piroctone Olamine is a product with antifungal and antibacterial activity. The product was developed by Hoechst AG in Germany between 1968 and 1977. The initial use of the product as an anti-dandruff active ingredient was in Germany in 1977 with a limited permit from the German authorities (BGA) for 3 years allowing a concentration in finished products of up to 0.5 %. In 1980, German authorities issued final approval for concentrations up to 1.0 % (in „rinse off“ formulations) and 0.5 % (in „leave on“ products). Approval in Europe was received in 1981/82, now reflected by the listing of piroctone olamine in the European Cosmetics Directive (Annex 6). The ingredient was approved in Japan in 1983 as a „quasi-drug“ for use as an anti-dandruff active ingredient.

It is common understanding in the scientific literature that products with an antidandruff activity control the growth of certain yeasts on the scalp, namely the *Malassezia* (earlier: *Pityrosporum*) species (E1,2).

## A. Individual Active components

Piroctone Olamine (brand name Octopirox®) is being used in the anti-dandruff application since the year 1977 with good results. During this time, the specifications and directions for use remained largely unchanged (see below under chapter VII).

Piroctone Olamine is an active ingredient with antifungal and antibacterial activity. Controlled studies as a single substance are available on the antibacterial and antifungal spectrum of piroctone olamine (E7,E8, E9) as well as on the substantivity of the substance on the scalp (E10). Stability studies were established over 3 years for the drug substance (E11) as well as in a finished shampoo (E12).

The scientific literature gives additional information on the antibacterial/antifungal spectrum (E13), substantivity on human hair (E14), thermostability (E15), photodegradation (E16) and analytical methods to determine the content of piroctone olamine in formulations (E17, E18, E19, E 20)

### **1. Controlled Studies**

#### Antibacterial spectrum

The antibacterial action, expressed by the minimum inhibitory concentration (MIC), was determined in the serial dilution test in a MUELLER HINTON medium at pH 7 (Difco Laboratories, Detroit, Michigan USA). Acetone/water was used as the solvent. The MIC values of piroctone olamine for the most familiar gram-positive and gram negative bacteria was in the range of 31.25 to 500 µg/mL (E7).

#### Antifungal spectrum

The antifungal action, expressed by the minimum inhibitory concentration (MIC), was tested in a Sabouraud dextrose test medium at pH = 6.5. Ethanol/water was used as the solvent. The MIC values of piroctone olamine for the most familiar species of fungi was in the range of 0.49 to 3.90 µg/mL (E8).

The antifungal action of piroctone olamine on the yeast *Pityrosporum ovale* was determined by Hänel to be between 62.5 and 125 µg/mL (E9). Due to the antagonistic effect of the growth medium on piroctone olamine, the real value was assumed to be approx. 6 µg/mL.

The antifungal action, expressed by the minimum inhibitory concentration (MIC), was tested on *Malassezia furfur* for several antifungal agents including piroctone olamine by A. Schmidt and B. Rühl-Hörster (E13) in a microtiter plate assay in a modified Leeming-

Notman medium. The MIC values of piroctone olamine were in the range of 16-64 µg/mL (E13).

#### Substantivity of piroctone olamine on hair and scalp

The substantivity of piroctone olamine on hair and scalp was determined by Futterer in 1976 (E10). A shampoo containing different amounts of piroctone olamine (0.2 %, 0.5 %, 1.0 %) was applied twice under practical conditions. The amount piroctone olamine absorbed on hair and scalp was determined by rinsing, analyzing the effluent and subtracting from the amount applied. The amount absorbed increased significantly with increasing concentration of piroctone olamine in the shampoo applied and reached 18 % at 1 % piroctone olamine concentration. On shaven heads (only scalp absorption) and an initial concentration of 0.46 % piroctone olamine in the shampoo, the amount absorbed was only approx. 10-20 %, compared to the value for absorption on hair and scalp.

The substantivity of piroctone olamine on human hair of caucasian and asian origin was determined by Löttsch and Herok (E14) by using radiolabelled piroctone olamine.

Under standard conditions (Shampoo containing 0.5 % piroctone olamine, application at 40 °C and pH = 7) the amount absorbed was similar for caucasian and asian hair. There was no significant dependence of substantivity between pH = 5 and pH = 8. On repeated application of the test shampoo absorption reached saturation after 15 applications. The absorbed amount after saturation was about 4 times the absorbed amount after one application. Addition of 1 % of low molecular or polymeric cationic products to the standard shampoo increased the substantivity of piroctone olamine significantly (see also E4 for reference).

Desorption of piroctone olamine by a successive treatment with cream rinse is low. The application of cream rinses after a treatment with a shampoo containing piroctone olamine does not significantly influence the substantivity.

Higher desorption was observed by using a plain shampoo without piroctone olamine. After 3 washings about 50 % were desorbed.

#### Stability testing

The stability of piroctone olamine was assessed by Futterer in 1981 (E11). No evidence of instability or decomposition could be detected after 3 years storage at room temperature (18-26 °C).

The stability of piroctone olamine in a shampoo formulation at 0.5 % (w/w) concentration was assessed by Futterer in 1981 (E12). Samples were stored at 18-26 °C in opaque plastic bottles. No evidence of instability or decomposition could be detected over the three years period.

#### Thermostability

The thermostability of several natural and synthetic antidandruff actives including piroctone olamine was studied by Coiffard et al (E15) in aqueous solution at pH around 7. Thermodegradation was studied at 50, 70 and 90 °C. The  $t_{90\%}$  value for piroctone olamine (time until 10 % of product are degraded) was extrapolated to be 190 days at 20 °C. This time was superior to the other active ingredients tested.

#### Photodegradation

The photodegradation of Piroctone Olamine was studied by Coiffard et al. (E16) by irradiating solutions of piroctone olamine in water and 3.5 % sodium lauryl ethersulfate. The degradation was first order kinetics and was slightly faster in surfactant solution than in water. The degradation was also pH-dependent with the highest rate constant at pH = 3.96. Rate constants were in the range of  $4.35-6.15 \cdot 10^{-3} \text{ min}^{-1}$ .

#### Analytical Methods

Determination of piroctone olamine in cosmetic products is described in the literature and can be done by HPLC (Gagliardi et al., E17, L. Chao, E18, Clariant procedure, E 20) or by a colorimetric method using the formation of a typically colored iron complex (Clariant method, E 19).

### **2. Partially Controlled or uncontrolled studies**

None

### **3. Documented Case reports. Identify expected or frequently reported side effects**

None

**4. Pertinent marketing experiences that may influence a determination on the efficacy of each individual active component**

The widespread use of piroctone olamine in antidandruff products worldwide may be seen as evidence for the well respected efficacy of piroctone olamine as anti-dandruff active.

**5. Pertinent medical and scientific literature**

Copies of pertinent literature are included in this submission (attachments E13 to E20). They are discussed under V.A.1.

## B. Combinations of the individual active components

Clariant is not seeking authorisation to use piroctone olamine in combination with other active ingredients.

The scientific literature shows, that the efficacy of antidandruff preparations containing piroctone olamine is depending on the overall formulation of the active. Cationic or zwitterionic components enhance substantivity of piroctone olamine and therefore also efficacy of antidandruff preparations containing piroctone olamine (E14).

The use of combinations of piroctone olamine and other well-known antidandruff actives (zinc pyrithione, climbazole, salicylic acid) is well documented in the scientific literature. As all of these literature studies were done in finished antidandruff formulations, these reports are listed in Chapter C (finished drug products). The TEA for piroctone olamine from 2003 shows that these combinations are used frequently in different countries to combat dandruff.

### **1. Controlled Studies**

none

### **2. Partially Controlled or uncontrolled studies**

none

### **3. Documented Case reports. Identify expected or frequently reported side effects**

none

### **4. Pertinent marketing experiences than may influence a determination on the efficacy of each individual active component**

The labelling information in the time and extent application for piroctone olamine from 2003 shows evidence that piroctone olamine may also be combined with other antidandruff actives. To our knowledge there have been no reports of negative effects through the use of combinations of piroctone olamine with other antidandruff actives.

### **5. Pertinent medical and scientific literature**

It was shown in the studies of Lötsch and Herok (E 14 and brochure E4) by radiolabelling, that the substantivity of piroctone olamine on hair is dependent on the overall formulation of the hair treatment composition. From E 14 it is evident, that the combination of piroctone olamine with cationic or zwitterionic surfactants (Betaines, Cetrimoniumchloride) or cationic

polymers (Polyquaternium-7, Polyquaternium-10; Table 4 in E 14) enhances the substantivity of piroctone olamine on the scalp and will therefore also improve the overall anti-dandruff effect of the respective cosmetic product.

### C. Finished drug products

Most efficacy studies on the activity of piroctone olamine in the anti-dandruff application were done in finished products like antidandruff shampoos, hair rinses (rinse-off) or hair tonics (leave-on), as the efficacy of an antidandruff treatment is not only dependent on the antifungal activity of the active principle, but also on its substantivity on the scalp and the behavior in the finished product. This is especially important in anti-dandruff shampoos, as the active has to show a significant substantivity to hair and scalp to be effective.

The effectiveness of products containing piroctone olamine in the anti-dandruff application is well documented for both rinse-off products like hair shampoos and hair rinses and for leave-on products like hair tonics. Effectiveness in both application forms is well documented through controlled studies (E 21-E 28) and scientific literature (E 29-E 43).

In rinse-off products efficacy data are available for concentrations between 0.3 and 1.0 % piroctone olamine. Controlled studies are available for concentrations between 0.3 and 0.75 % (E 21- E 28).

In leave-on products like anti-dandruff tonics efficacy data are available for a concentration of 0.1 % piroctone olamine in a controlled study (E 25) and scientific literature based on that original study (E 33).

The controlled studies and the studies in the scientific literature were done either in comparison to placebo products or in comparison to other well-known actives like zinc pyrithione, magnesium pyrithione, climbazole, ketoconazole, coal tar etc.

The controlled studies were mainly done on caucasian hair (studies in UK E22-25, Germany E 28 and Switzerland E 26), but there is also one controlled study (E 27) and scientific literature (E 31) on asian hair and scalp available.

All studies show, that piroctone olamine is effective in reducing dandruff vs. blind control. A minimum concentration of 0.3 % of piroctone olamine in rinse-off products like shampoos still gives significant anti-dandruff efficacy (E 28). However, the anti-dandruff effect increases with increasing concentration and was recommended to be at least 0.5 % (E29). 1.0 % gives optimal effect. In leave-on products 0.1 % of piroctone olamine are already sufficient to give a significant effect (E 33).

The scientific literature shows a variety of additional efficacy studies. Combinations of piroctone olamine with additional anti-dandruff actives were assessed (E 35, E 36, E 37, E 40, E 43).

## 1. Controlled Studies

### Efficacy studies in rinse-off applications (shampoos, hair rinses)

Piroctone Olamine was tested by Futterer and Jänner (E 21) for its anti-dandruff efficacy between 1971 and 1974 in Germany. A total of 168 test persons received piroctone olamine (Octopirox®) in shampoo bases ineffective to dandruff on one side of the head against shampoo bases containing the monographed zinc pyrithione (or zirconium pyrithione) as a standard on the other side of the head. Both actives were applied at 0.5 % concentration in a shampoo base. Piroctone olamine showed an equally good anti-dandruff efficacy compared to the reference compounds (E21, Appendix 2,3,4) or slight performance advantages (Appendix 5). No signs of intolerance were noted for both test substances.

Life Science Research (UK) studied in 1980 (E 22) the efficacy of a shampoo containing piroctone olamine (0.75 %) and a shampoo without anti-dandruff active using the half-head technique on 32 subjects. The mean dandruff score was measured (area x severity). After six weeks of treatment the mean dandruff score associated with piroctone olamine had decreased from 24.4 to 11.1, a decrease, which was highly significant. The reductions after two and four weeks were also highly significant. For the inactive shampoo this value had increased from 24.3 to 26.7 at the same time. In the comparison of shampoo containing Octopirox and the inactive shampoo, the difference in the dandruff score between shampoo containing piroctone olamine and the inactive shampoo was highly significant as well.

Life Science Research (UK) studied in 1981 (E 23) the efficacy of a shampoo containing piroctone olamine (at 0.75 %) and a shampoo with the anti-dandruff active Climbazole (at 1 %) using the half-head technique on 32 subjects. The mean dandruff score was measured (area x severity). After six weeks of treatment the mean dandruff score associated with piroctone olamine at 0.75 % revealed a reduction of 51.4 %, compared with a reduction of 44.2 % associated with Climbazole shampoo at 1 %. Both reductions were highly significant. Piroctone Olamine appeared to be associated with an earlier improvement in loose dandruff than the Climbazole shampoo, but no difference between treatments was apparent in relation to adhering dandruff.

Life Science Research (UK) studied in 1984 (E 24) the efficacy of a shampoo containing piroctone olamine (at 0.75 %) and a shampoo with the anti-dandruff active DTPD/MgSO<sub>4</sub>

(dipyrithione magnesium sulfate, at 1 %) using the half-head technique on 34 subjects. The mean dandruff score was measured (area x severity). After six weeks of treatment after a pretreatment phase with inactive shampoo the mean dandruff score associated with piroctone olamine at 0.75 % was reduced from 19.5 to 11.3, compared with a reduction from 19.3 to 14.7 (23.8 % reduction) with DTPD/MgSO<sub>4</sub> (at 1 %). The differences between the mean dandruff scores were statistically significant after 6 weeks of treatment. An overall reduction was recorded in the subjects assessment of scalp itching. 0.75 % piroctone olamine shampoo was associated with a slightly greater reduction (47.1 %) than DTPD/MgSO<sub>4</sub> (at 1 %) shampoo (41.2 %) after six weeks of treatment.

Cosmital SA (Switzerland) conducted a comparative study of two antidandruff shampoos containing 0.3 % piroctone olamine (Octopirox) and 0.5 % Climbazole, respectively in 1994 (E 26). The study was done on 10 volunteers each for both products. The study consisted of a pretreatment phase of 4 weeks using an inactive shampoo, a treatment phase of 5 weeks with the active shampoos and a posttreatment phase of 3 weeks with a shampoo without active. The judgement was made by assessing the man dandruff area by image analysis. The study showed, that both shampoos revealed a significant anti-dandruff effect after 3 weeks (6-7 treatments), which survived up to two weeks after stopping the treatment. No significant difference between 0.3 % piroctone olamine and 0.5 % climbazol could be detected.

Hoechst AG and Parexel GmbH studied the action of piroctone olamine shampoo (0.75 %) under tropical conditions in Thailand against zinc pyrithione (1.0 %) and Climbazole shampoos (0.75 %) in the treatment of seborrhoeic dandruff of the scalp in Asian population (E 27) on 288 volunteers. The survey consisted of a 3-week vehicle run-in phase, a 5 week treatment period and a two-week follow-up period. The experimental period of the survey was performed using a randomized, double blind parallel design with 4 groups (piroctone olamine, zinc pyithione, climbazole, no active).

After 5 weeks of treatment, about 70 % of the subjects in all active treatment groups presented with dandruff score „none“ or „slight“. By contrast, the corresponding figure for the vehicle (without active) was below 53 %. In the piroctone olamine group more than two thirds (69.0 %) of the subjects improved to „none“ or „slight“ at the end of the treatment. This was similar to the other two active groups. The beneficial effect of piroctone olamine treatment was particularly marked for severe cases of seborrhoeic dandruff.

ProDerm (Germany) conducted a clinical study to evaluate the anti-dandruff efficacy of shampoos containing piroctone olamine (0.3 %) and zinc pyrithione (0.3 %) (E 28) on 51 panellists in 2000.

The panellists used a placebo shampoo for two weeks. Afterwards each panelist used product A (containing 0.3 % piroctone olamine) or (containing 0.3 % zinc pyrithione) B for a period of 4 weeks at open usage frequency. Before and after the 4 weeks usage period, scalp scales were combed out of the panelist's hair in a standardized fashion for quantification (image analysis and weight). Additionally, panelists were asked for their opinion on the anti-dandruff effect of the shampoo and were questioned for subjective symptoms like itching and burning. Both products were found to reduce the weight of scalp scales and the area of dandruff significantly. For both products an improvement of scalp scale related symptoms was noted. Product A containing piroctone olamine at 0.3 % gave a reduction of scalp scale weight from 5.52 to 2.33 mg after the treatment period, vs. 9.57 to 2.11 mg for the product containing zinc pyrithione. The high baseline for the zinc pyrithione group was a result of three panelists in group B with extremely high amounts of scalp scales. For both shampoos a significant anti-dandruff effect was determined.

Dietrich and Böllert (E 29) described in 1980 the half-head technique to assess the efficacy of anti-dandruff shampoos. As actives piroctone olamine (1.0 %, 0.5 %, 0.2 %) and zinc pyrithione were used (1.0 %, 0.5 %), also compared with an inactive shampoo. For assesment a dandruff scale between 0 and 3 was used. With 1 % piroctone olamine or zinc pyrithione the shampoos exhibit very good anti-dandruff effect. The authors recommend for highly efficient anti-dandruff shampoos a minimum of 0.5 % piroctone olamine or zinc pyrithione. In direct comparison, the results for piroctone olamine were slightly more favorable than for zinc pyrithione.

Futterer (E 30) described in 1981 the evaluation of anti-dandruff products with the half-head technique. Data are given for shampoos and cream rinses containing piroctone olamine and zinc pyrithione. Examples are given for:

- a) a shampoo with 0.75 % of piroctone olamine versus placebo
- b) a cream rinse containing piroctone olamine at 0.3 % vs. placebo after shampooing with a shampoo containing 0.2 % of piroctone olamine
- c) shampoos containing piroctone olamine or zinc pyrithione at 0.5 %
- d) shampoo containing 0.75 % piroctone olamine vs. 0.5 % zinc pyrithione

Piroctone olamine exhibited excellent antidandruff effect, which surpassed the effect of zinc pyrithione.

In a series of three publications Watanabe et al. (E 31) evaluated the efficacy of hair shampoo and hair rinses containing piroctone olamine using the half-head technique in Japan.

Piroctone olamine shampoos containing 1.0 % and 0.75 % active ingredient were significantly more effective than a shampoo containing 1 % of zinc pyrithione in a study on 48 volunteers. Also a hair rinse containing 0.3 % of piroctone olamine was significantly more active than a hair rinse containing 0.3 % of zinc pyrithione. Both active shampoos (piroctone olamine and zinc pyrithione) produced a significant decrease in the grade of dandruff two weeks after onset of application. Regarding the itching effect, shampoos containing 0.75 or 1 % of piroctone olamine were significantly more effective than shampoos containing 1 % of zinc pyrithione. In an investigation on 23 subjects with scalp diseases, there was no incidence of side effects such as irritation, redness, baldness or swelling. Improvement rates in dandruff and itching were high.

Futterer (E 32) reviewed efficacy studies based on half head tests in double-blind-studies.

In a study on 32 subjects a shampoo containing 0.75 % of piroctone olamine was tested against a placebo shampoo. After six treatments in six weeks the piroctone olamine shampoo treatment resulted in a decrease of dandruff symptoms of 54.5 %, versus 9.9 % for the placebo.

In another study comparing a shampoo containing 0.5 % piroctone olamine and a shampoo containing 0.5 % of zinc pyrithione, both active substances caused a rapid reduction in the degree of dandruff, with piroctone olamine exerting a markedly better effect. The change in dandruff score was 81.7 % for piroctone olamine and 68.6 % with zinc pyrithione, respectively.

Saint-Leger (E 34) et al. explored the link between scalp microflora and anti-dandruff treatment with piroctone olamine and magnesium pyrithione. Piroctone olamine was more effective than magnesium pyrithione in reducing scalp scaling. Piroctone olamine was notably able to cause regression of dandruff more swiftly. Dandruff was decreasing, when the population with *Pityrosporum ovale* was decreased by treatment with piroctone olamine or magnesium pyrithione.

Pierard-Franchimont (E 35) conducted a randomized, double-blind clinical study comparing a non-tar-shampoo containing 2 % of salicylic acid, 0.75 % of piroctone olamine and 0.5 % elubiol versus a 0.5 % coal tar shampoo. The clinical evaluation showed that the non-tar shampoo was as effective as the tar shampoo, with both receiving high approval ( $\geq 70$  %) ratings. The non-tar shampoo yielded a significantly higher reduction of *Malassezia* sp. counts during the treatment phase.

Montesion et al. (E 36) evaluated the synergism of piroctone olamine with  $\alpha$ - and  $\beta$ -hydroxyacid esters in antidandruff shampoos (C12-13 alkyl lactate and tridecyl salicylate). Shampoos were applied for 4 weeks twice a week. Dandruff weight, dandruff size and corneocyte count were evaluated. The authors found similar antidandruff efficacy for a shampoo containing 0.5 % of piroctone olamine only compared to a shampoo containing a combination of 0.2 % of piroctone olamine and either 0.5 % of tridecyl salicylate or C12-13 alkyl lactate. The hydroxyacid esters alone were inactive.

Loden et al. (E 37) compared two shampoos in a double-blind, randomized bilateral study on 19 subjects comparing a shampoo containing a combination of 0.75 % of piroctone olamine and 2 % of salicylic acid versus a shampoo containing 1 % zinc pyrithione. Both shampoos were highly effective in treating dandruff. The combination of piroctone olamine and salicylic acid appeared to be slightly more effective in reducing dandruff compared to the shampoo containing 1 % of zinc pyrithione.

In a product brochure from 2000 Procter&Gamble (E 38) show results from a study on 467 patients in 1994 to assess efficacy of shampoos containing 1 % of zinc pyrithione versus 0.85 % of piroctone olamine. The limit of no visible flaking was achieved after approx. 3 weeks treatment for both shampoos, 1 % zinc pyrithione reaching the limit slightly faster than 0.85 % of piroctone olamine (p. 2).

Pierard-Franchimont (E 39) explored the connection between hair shedding and anti-dandruff treatments comparing shampoos containing 1 % ketoconazole, 1 % piroctone olamine and 1 % of zinc pyrithione in a study over 6 months.

The three treatments cleared pruritus and dandruff rapidly. At end point, hair density was unchanged, although hair shedding was decreased and the anagen hair percentage was increased. The effect on the mean hair shaft diameter was contrasted between the treatments

(ketoconazole + 5.4 %, piroctone olamine + 7.7 %, zinc pyrithione -2.2 %). Telogen effluvium was controlled by ketokonazole, piroctone olamine and zinc pyrithione. Ketoconazole and piroctone olamine increases the mean hairshaft thickness while discretely decreasing the sebum output at the skin surface.

Humke et al (E 40) compared the anti-dandruff efficacy of ketoconazole (2 %) versus the complex saliker (2 % capryloyl glycine, 1.3 % salicylic acid, 1 % piroctone olamine , 0.2 % glylcacyl, 0.1 % capryloyl salicylic acid) in shampoos. The study involved 50 patients and a treatment time of four weeks. The two shampoos were well tolerated. The tolerance of saliker was judged to be excellent by 28 % of the volunteers vs. only 8 % for the ketoconazole shampoo. The assessment of the global efficacy indicated that saliker shampoo was superior to the ketokonazole shampoo.

Pierard-Franchimont et al. (E 41) conducted a study comparing shampoos containing 1 % of ketoconazole versus 1 % of piroctone olamine to assess the effect of residence time of the shampoo on the efficacy of antidandruff shampoos. Two groups of each 21 panelists with severe dandruff were involved. In each group intradivisional comparisons were made by a split-scalp design between the effect of a 5 min residence time versus no residence time. Both shampoos induced significant reductions in scaliness and yeast colonisation. The beneficial effects were obvious immediately after one single shampooing and 3 days later as well. The improvement was better with 5 min residence time. The piroctone olamine treatment benefited more than the ketoconazole treatment from the extension of residence time.

In an internet advertisement Wella (E 42) describes the beneficial effect of a combination of the anti-dandruff actives Octopirox (piroctone olamine), climbazole and zinc pyrithione in the treatment of dandruff.

Bartalini et al. (E 43) conducted an anti-dandruff study on 30 subjects with shampoos containing 0.5 % of piroctone olamine and a lotion containing 0.3 % of piroctone olamine. In the study, which lasted 30 days, the subjects used lotion and shampoo in the first 11 days, then only shampoo. All the subjects treated showed a marked improvement in both objective and subjective terms. In addition, all the patients showed optimum toleration of the products. A high antipityriasis activity was proven.

### **Efficacy studies in leave-on applications (hair tonics)**

Life Science Research (UK) studied in 1986 (E 25) the efficacy of hair tonics containing piroctone olamine vs. placebo hair tonics on 107 volunteers. One group of 53 subjects used a hair tonic HAG 099C (without active ingredient) and the second group of 54 volunteers used a hair tonic HAG 099D (with 0.1 % of piroctone olamine). Treatment involved twice-weekly washing with a bland shampoo followed by two 10 mL applications of the test hair tonic for six weeks. Dandruff was assessed on a 0-80 scale, 28 days before the start of treatment, on the day before first treatment and on days 14, 28 and 42. Neither the subjects nor the examiners were aware of the identity of the products. Using statistical analysis hair tonic HAG 099D (containing 0.1 % of piroctone olamine) showed a significantly greater reduction in dandruff score than HAG 099C after 28 and 42 days treatment. After 42 days, the dandruff score reductions were 17.8 % for HAG 099C and 49.3 % for HAG 099D.

Futterer (E 33) described the evaluation of piroctone olamine in hair tonics. In two groups of approx. 50 persons two hair tonics were applied for 4 weeks, one containing 0.1 % of piroctone olamine, the other without active substance. Piroctone olamine incorporated into a hair tonic at 0.1 % concentration exhibited satisfactory antidandruff efficacy. The reduction of dandruff score after day 42 of the treatment was 49.3 % for the tonic containing piroctone olamine and only 17.8 % using non-active hairtonic. In contrast to shampoos and hair rinses the use of antidandruff actives in hair tonics is seen as the most effective way to control dandruff.

### **2. Partially Controlled or uncontrolled studies**

none

### **3. Documented Case reports. Identify expected or frequently reported side effects**

none

### **4. Pertinent marketing experiences than may influence a determination on the efficacy of each individual active component**

none

**5. Pertinent medical and scientific literature**

Copies of pertinent literature are included in this submission (attachments E29 to E43). They are discussed under V.C.1.

**VI. A summary of the data and views setting forth the medical rationale and purpose (or lack thereof) for the drug and its ingredients and the scientific basis (or lack thereof) for the conclusion that the drug and its ingredients have been proven safe and effective for the intended use. If there is an absence of controlled studies in the material submitted, an explanation as to why such studies are not considered necessary must be included.**

Control of Dandruff is an important issue from a hygiene standpoint and is also important in view of the well-being of the population. Based on the data presented herein piroctone olamine may be regarded as safe and effective in the anti-dandruff application. State of the art antidandruff agents are partially limited in their scope of application due to restraints in their physical properties (i.e. some monographed anti-dandruff agents are not sufficiently soluble in the base matrix) and cannot be used e.g. in anti-dandruff lotions. Piroctone olamine additionally has an improved safety standard compared to existing products. It can therefore be concluded that the inclusion of piroctone olamine into the anti-dandruff monograph is justified.

Octopirox, the ethanolamine salt of a substituted pyridone (1-hydroxy-4-methyl-6 (2,4,4-trimethylpentyl)-2 (1H)), is also known by the international non-proprietary name of piroctone olamine. Octopirox is used as an anti-dandruff agent since 1977 in Western Europe, Eastern Europe, Africa, Asia including Japan, Middle and South America, and no negative side effects have occurred. However, because of the proposed use as an anti-dandruff agent, Octopirox was evaluated in an extensive series of studies designed to establish its safety. The appropriateness of the animal studies is supported by the fact that Octopirox itself does not appear to be metabolized and is subject to relatively rapid excretion; that is, it does not accumulate.

The cumulative data amassed during the toxicological evaluations demonstrate that Octopirox has an extremely low order of toxicity. According to results from acute studies, Octopirox is practically non-toxic (LD50 = 8100 mg/kg body weight orally in female rats; LD50 > 4000 mg/kg body weight orally in female beagle dogs; LD50 >2000 mg/kg body weight dermally in female rats; LC50 ≥ 4.9 mg/l inhalative in rats).

Based on a primary dermal irritation test on rabbits, pure Octopirox must be regarded as an irritant to skin. However, under practical conditions of use, Octopirox exhibits a good skin tolerance in animals as well as in human volunteers and a good eye mucous membran

tolerability. Octopirox does not induce any signs of sensitization in animals as well as in human beings and does not cause photosensitization. In all of the subchronic in-life studies on Octopirox the no-effect-level (NOEL) was consistently placed at or above 100 mg/kg body weight or > 29000 times the exaggerated human exposure when using a shampoo containing 1 % Octopirox. In addition, regarding subacute and subchronic studies, Octopirox does not show any symptomatology which gives evidence for a specific organ toxic effect either after oral or dermal application. This is valid especially for the dermal exposure route as could be seen in long-term dermal toxicity studies (6 and 12 month) which does not disclose any toxic effect prohibitive for use of Octopirox in concentrations of up to 1 %. Mutagenicity assays, both in vitro and in vivo revealed no genotoxic potential. Additionally, Octopirox does not disclose any indication on a very low limit of detection for a genotoxic activity in vivo mediated by DNA binding after subcutaneous administration. Taking into account practical exposure conditions of Octopirox, none of the available data indicates a carcinogenic risk of this substance. Octopirox, in doses as high as 2000 mg/kg body weight, was devoid of embryo- or fetotoxicity or teratogenic potential in different species using different routes of application.

A wide variety of possible pharmacologic effects of Octopirox was investigated with both in vivo and in vitro techniques. All produced negative results suggesting that the substance is pharmacologically relatively inert. Extensive pharmacokinetic studies and investigations on dermal absorption revealed low skin penetration activity of Octopirox, especially after rinsing. The body burden for a 55 kg woman was calculated to be 3.4 µg/kg from one application of shampoo containing 1 % Octopirox with subsequent rinsing. Based on the NOEL's of Octopirox found in subchronic 90-day feeding studies in rats and beagle dogs, this results in a safety factor of 29400 (Black and Kamat, 1988; Submission No. R51). Even when using leave-on formulations containing 1% Octopirox (non-occlusive conditions), this safety factor is calculated to be greater 2600. It is concluded, based on the available toxicologic, pharmacologic and pharmacokinetic data, on the large safety factors calculated, as well as on the existing marketing experiences on Octopirox, that the possibility of systemic toxicity resulting from the use of leave-on or rinse-off products containing 1 % Octopirox is remote.

From the efficacy studies and literature presented it can also be concluded that piroctone olamine may be considered as effective in the antidandruff application.

Piroctone Olamine is substantive on hair and is active against fungi and yeasts, which are regarded to be responsible for the evolution of dandruff. Piroctone Olamine is very stable on

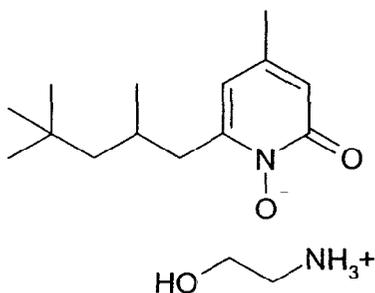
storage as a single component and also dissolved in cosmetic base matrices. Efficacy in products intended to be rinsed off (hair shampoos and hair rinses) as well as in products intended to be left on the scalp (hair tonics) could be demonstrated in controlled studies and is documented in the scientific literature. In comparison with active ingredients already monographed, piroctone olamine showed equal or even better results in controlled studies.

**VII. An official United States Pharmacopeia (USP)- National Formulary (NF) drug monograph for the active ingredient or a proposed standard for inclusion in an article to be reorganized in an official USP-NF drug monograph. Include information showing that the official or proposed compendial monograph for the active ingredient is consistent with the active ingredient used in the studies establishing safety and effectiveness to a material extent and for a material time. If differences exist, explain why.**

Clariant proposes the following standard for piroctone olamine:

Proposed OTC Monograph for Piroctone Olamine (Octopirox®):

Piroctone Olamine



$C_{14}H_{23}NO_2 \cdot C_2H_7NO$

1-Hydroxy-4-methyl-6(2,4,4-trimethylpentyl)2-pyridon monoethanolamine salt (68890-66-4)

Piroctone Olamine contains not less than 98.0 percent and not more than 101.5 percent of  $C_{14}H_{23}NO_2 \cdot C_2H_7NO$ , calculated on the dried basis.

**Packaging and storage** - Preserve in well-closed containers, protected from light.

**Identification** –

white to slightly yellowish-white crystalline powder

**A: Infrared Absorption:**

The maxima in the spectrum of the substance correspond with respect to position and relative intensity to those in the spectrum of the reference standard

**B: Ultraviolet Absorption**

*Solution:* 30.0 mg per 100.0 mL of medium; dilute 5.0 mL of this solution to 50 mL of medium.

*Medium:* 0.1 N solution of sodium hydroxide in methanol

Measure absorption at absorption maximum at 317  $\pm$  2 nm; specific absorbance in the maximum at 317 nm: 214 to 236, calculated with reference to the dried substance.

**C: TLC <621>:**

Compare the chromatograms obtained in *Chromatographic purity*.  $R_f$  values of the principal spots of *Test solution* and *Standard solution* are identical.

**D: Appearance of solution:**

*Solution:* dissolve 1.0 g of substance in 10 mL methanol.

The solution is clear, not more intensely colored than reference solution Y<sub>5</sub>

E: Melting range <741>: between 133-136 °C (under decomposition)

**pH <791>:**

*Solution:* 1.0 g of substance is shaken with 100 mL of water for 1 min.

The pH-value is between 8.5 and 10.0

**Chromatigraphic Purity-related substances**

*Test solution:* 400.0 mg of substance are dissolved in 10.0 mL of methanol.

*Standard solution:* 400.0 mg of Piroctone Olamine reference standard are dissolved in 10.0 mL of methanol. 0.5 mL of this solution are diluted with methanol to 100.0 mL.

*mobile phase:* Prepare a solution of 40 parts 0.2 M sodium editronate (dissolve 74.45 g of sodium editronate and 10.0 g sodium hydroxide to 1000 mL solution in water), 37 parts of methanol, 21 parts of acetone and 2 parts of 26 % ammonia solution.

*stationary phase:* Polyamide TLC-glass plates (e.g. Polyamid 11F, Merck)

*Procedure:* apply each 10 µL portions of *Test solution* and *Standard solution* to the *stationary phase*. Allow the separate spots to dry and develop the chromatogram until the solvent front has moved approximately 15 cm. Remove the plate from the developing chamber, mark the solvent front, allow the solvent to evaporate and examine the plate under UV light of 254 nm; the chromatograms show principal spots at about the the same Rf value.

*System suitability:* From the chromatograms obtained as directed in *Procedure*, estimate the intensity of any other spots beside the main spot of the *test solution*. The system is satisfactory if any other spot beside the main spot of the *test solution* is less intense than the main spot of the *standard solution*.

**Heavy Metals <231>:** not more than 10.0 µg/g

**Loss on drying <731>** - Dry 1.0 g of substance in a vacuum at room temperature for 6 hours at a pressure of 1.5-2.5 kPa. It loses not more than 0.3 % of its weight.

**Residue on Ignition <281>:** no more than 0.2 % (sulphated ash).

**Monoethanolamine assay:**

Dissolve approx. 0.2000 g of dried substance in 40 mL of anhydrous acetic acid and titrate with 0.1 N perchloric acid in waterfree medium, determining the endpoint potentiometrically.

The percentage of monoethanolamine corresponds to  $V \times F \times 6.108 \times 10 : (E \times (100 - T))$

V = consumption 0.1 N perchloric acid in mL

F = correction factor of perchloric acid solution

E = test substance in g

T = loss on drying

The content of monoethanolamine must be between 20.1 to 20.9 %,calculated with reference to the dried substance

**Assay:**

*Determination of the factor of sodium hydroxide solution:*

approximately 0.1000 g of benzoic acid standard are dissolved in 20.0 mL of methanol. 20.0 mL of deionized water are added and titrated potentiometrically with 0.1 N sodium hydroxide solution.

The factor F is determined by  $F = E_B \times 1000 : ((V-V_B) \times 12.212)$

E<sub>B</sub>: weight of benzoic acid standard

V: usage of 0.1 N sodium hydroxide solution

V<sub>B</sub>: usage of 0.1 N sodium hydroxide solution in a blind test without benzoic acid.

*Procedure:*

approx. 0.2000 g of dried test substance are dissolved in 20.0 mL of methanol. 20 mL of deionized water are added. Titrated the solution immediately with 0.1 N sodium hydroxide solution, determining the endpoint potentiometrically.

The assay of piroctone olamine in % is:

$$\text{Assay} = (V - V_B) \times F \times 29.84 \times 10 : (E \times (100 - T))$$

V = usage of 0.1 N sodium hydroxide solution

V<sub>B</sub> = usage of 0.1 N sodium hydroxide solution in a blind test

The assay must be between 98.0 to 101.5 %, calculated with reference to the dried substance.

To demonstrate that the proposal for the OTC monograph corresponds to the product, which has been tested for safety and efficacy, quality control sheets, specifications and product data sheets from the years 1974-2001 are presented.

The safety testing was conducted starting on 20.10.1974 (study R1 on oral toxicity) until 1986 (study R 3) with the main studies being conducted between 1977 and 1979. Efficacy testing with the controlled studies presented herein was done between 1978 (E 21) and 2000 (E 28).

Piroctone Olamine (brand name Octopirox®, Clariant GmbH, formerly Hoechst AG, initial product development code H 72 6146 A) is being used in the anti-dandruff application since the year 1977. Until mid of the 1990's Hoechst AG was the sole supplier for piroctone olamine on a global basis. It can therefore be concluded that also the literature studies were conducted with the product described herein. During this time, the purity requirements and directions for use remained largely unchanged. Based on the first analytical procedures from 1974 which already assured identity of the product, later on only due to improved analytical methods additional parameters were included in the specification.

For reference a quality control sheet from 18.02.1974 (E 44), a certificate of analysis from 10.09.1975 (E 45), a certificate of analysis from 16.01.1976 (E 46) and a product information sheet from 1976 (E 47), specifications for Piroctone Olamine from 1983 (E5) and 2001 (E6), product information sheets from 1976 (E 46) and product brochures from 1991 (E3) and July 2003 (E4) are attached.

The proposal for the OTC monograph is based on the current specification for piroctone olamine (Octopirox®), which is in place since 2001.

The first quality control sheet from 1974 (E 44) from the development phase of substance H 72 6146 A, which is identified in E46 as Octopirox ® (brand name of Clariant GmbH (formerly Hoechst AG) for piroctone olamine) does not list all parameters of the specification from 1983 and 2001 and the current proposal for an OTC monograph, as the product was still in the development phase.

However it already contains substantial information, which clearly shows, that the material is identical to the product quality described in the later specifications and the proposal for the OTC monograph.

In detail the following parameters for identification are listed in E44:

- solution of 1 g product plus 10 mL of Methanol (point 3)

- pH = 9,0 (point 22)
- melting point 133 °C (point 33)
- residue on ignition (ash) < 0.1 % (point 26)
- water content < 0.1 % (point 29)
- active content (point 51) is 99.4 %; the explanatory chart attached indicates the titration with lithium methylate as titration agent
- TLC (point 50) indicates that the product is homogenous according to the TLC
- extinction (point 44) is measured at 304 nm, which is different from the method in use nowadays; this method was changed around 1980 to the measurement at 317 nm to improve the reproducibility of the results.

The certificate of analysis from 1975 (E 45) lists very similar analytical data, it especially lists the active content to be 100.1 %.

The certificate of analysis from 16.01.1976 (E 46) lists the active content determination on the dried substance to be 100.0 %. It also shows the determination of aminoethanol (20.48 %), which has been used since then for additional characterisation and also still matches the purity requirements existing nowadays.

The product information from 1976 (E 47) identifies product H 72 6146 as Octopirox and gives the molecular structure.

The comparison of the specification from 1983 (E5) and 2001 (E6) is summarized below:

Piroctone Olamine is a white to yellowish-white crystalline powder (E5,E6) which is clearly soluble in methanol (E5,E6) and identified by TLC (E5,E6). The melting point (under decomposition) is given with 130-135 °C (E3) and 133-136 °C (E4, E6). Loss on drying is given with < 2 % (E5) and < 0.3 % (E6). Sulphated ash is given with < 0.2 % (E5,E6).

The monoethanolamine content is determined by potentiometric titration with perchloric acid. The specification limits for monoethanolamine content were unchanged between 1983 and 2001 (20.1-20.9 %) and were already measured in 1976 (E5,E6).

The active content is determined by potentiometric titration with a base to be 98.5-101.5 %. Between 1983 and 2001 these purity requirements remained unchanged. Only the titration agent was changed from lithium methylate to sodium hydroxide solution in order to lower analytical cost.

The specific extinction in solution is determined at 317 nm to be 214-236 in 0,1 N methanolic sodium hydroxide solution (E5,E6).

Based on the evidence presented, it can therefore be concluded that the active ingredient piroctone olamine remained unchanged in quality and purity from the time, when safety and efficacy data were prepared.

### **Adverse Drug Experience Information**

(pursuant to 21 C.F.R. § 330.14 (f) (2)):

In most parts of the world, anti-dandruff products (including piroctone olamine) are regulated as „cosmetics“ and not „drugs“. To the best of Clariant’s knowledge, piroctone olamine is not marketed as a prescription drug in any country. Even in countries where piroctone olamine may be regulated as over-the-counter (OTC) drug, Clariant has no knowledge of, or information about, any adverse drug experiences associated with this active ingredient.

**Environmental Assessment**

Clariant believes, and hereby claims, that the requested action qualifies for a categorical exclusion from the environmental assessment requirements under 21 CFR 25.31 (b).