SUMMARY OF PRODUCT CHARACTERISTICS

TRICLONAM ELIXIR
TRICLOFOS SODIUM 500 MG / 5 ML

Treatment Matters

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1. Therapeutic indications
Insomnia, daytime sedation and pre-medication in EEC.

2. Dosage and Administration

For insomnia:
Adults and children over 12 years: 10 ml daily, in certain cases a higher dosage may be required - up to 20 ml daily.
Children 6-12 years: 5-10 ml daily.
Children 1-5 years: 2.5-5 ml daily.
Infants up to 1 year: 1-2.5 ml daily.
As a sedative:
Adults and children over 12 years: 5 ml twice daily.
Children 6-12 years: 5 ml daily.
Children 1-5 years: 2.5 ml daily.
Infants up to 1 year: 1 ml daily.

3. Clinical Results

(1) Clinical Data Package
None

(**2) Clinical Effects**
Clinical results judging by sleeping effects were 84.3% (321/381).

(3) Clinical Pharmacological Test
No applicable data

(4) Exploratory Test
No applicable data

(5) Verification Test

1) Randomized Parallel Dosage Response Study
No applicable data

2) Comparative Test
The following results were obtained comparing chloral hydrate (22mg/kg) and triclofos sodium (33mg/kg) in 71 children aged 4 to 14 years old who require sedation during EEG. EEG was used for the sleep start monitor.

		Triclofos Sodium syrup (37 subjects)	Chloral hydrate (34 subjects)
Dosage*		Average 1 g (480 mg to 1960 mg)	Average: 680 mg (300mg to 1,510mg)
Sleep introduction time		37.3 ± 12.1 minutes	36.6 ± 14.4 minutes
Ineffective cases		6 cases	4 cases
Taste	Aversion	2 cases (5%)	9 cases (27%)
	Good	14 cases (33%)	11 cases (32%)
	Very good	21 cases (51%)	14 cases (41%)
Adverse reactions		16 types in 9 people (24%)	16 types in 9 people (26%)

*: Dosage is expressed in the amount of the active ingredient.
Triclofos Sodium Syrup active ingredient: Triclofos sodium
Chloral hydrate active ingredient

3) Safety Test
No applicable data

4) Testing by patient/condition
No applicable data

(6) Therapeutic Use

1) Treatment outcome study and research of specific uses (special survey)/Clinical studies after manufacturing and sales (post-marketing clinical results)
No applicable uses

2) Approval conditions of details for execution or overview of the executed testing
None

Pharmacology Matters

1. Pharmacologically-related Chemical Compound or Compound Group

Chloral hydrate

2. Pharmacological Action

(1) Site and mechanism of action

Site of action:	Reticular of brainstem
Mechanism of action:	Inside the body, it becomes the metabolite trichloroethanol, in the same way chloral hydrate does, and exhibits sedation and hypnotic activity. There is less gastrointestinal irritation than with chloral hydrate.

(2) Study results that support drug efficacy

See Treatment Matters I-2. Pharmacological Action (3) Onset time/duration of action

(3) Onset time/duration of action

Onset time of action

Within 60 minutes

Fell asleep within 30 minutes of administration:	381/1075 cases (35.4%)
within 45 minutes:	818/1075 cases (76.1%)
within 60 minutes:	1011/1075 cases (94.0%)

Duration of action:

Action lasted 2 to 3 hours in the highest amount of cases

Out of 295 pediatric cases, sleep duration was 2 to 3 hours in 41.7% (123), 5 to 6 hours in 14.2% (42) and at least 2 hours in 68.8% (203) of cases.

Out of 143 adult cases, sleep duration was at least 2 hours in 62.9% (90) of cases.

Pharmacokinetic Matters

1. Change in Blood Concentration and Method of Measurement

(1) Blood concentration effective in treatment

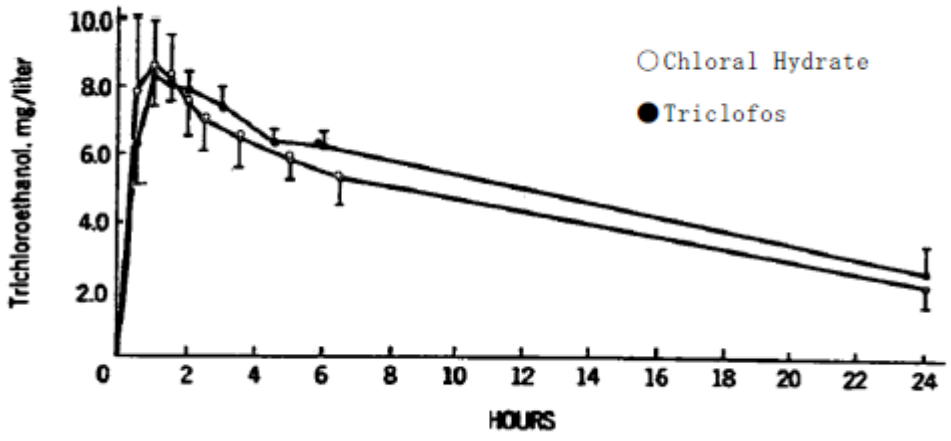
No applicable data

(2) Time to reach peak blood concentration

About 1 hour

(3) Blood concentration confirmed in clinical trials

Blood concentration of trichloroethanol when a 22.5 mg/kg dose was administered orally to a healthy adult (n=7) reached a peak of 8.2 ± 0.6μg/mL one hour after administration, with a half-life (T1/2β) of 8.2 hours. 4)



(4) Toxicity Zone

No applicable data

(5) Effects of diet and concomitant drugs

No applicable data

(6) Pharmacokinetic variability factors found by population analysis

No applicable data

2. Pharmacokinetic Parameters

(1) Analysis method

No applicable data

(2) Absorption rate constant

No applicable data

(3) Bioavailability

No applicable data

(4) Elimination rate constant

No applicable data

(5) Clearance

No applicable data

(6) Distribution volume

No applicable data

(7) Blood plasma protein coupling

35%

3. Absorption

Absorption site: Stomach

4. Distribution

(1) Permeability of blood-brain barrier

High (permeates)

(2) Permeability of blood-placental barrier

High (permeates)

(3) Transferability to breastmilk

No applicable data

(4) Transferability to cerebrospinal fluid

No applicable data

(5) Penetrability to other tissue

No applicable data

5. Metabolism

(1) Metabolic site and metabolic pathway

Trichloroethanol is metabolized by trichloro acetic acid in red blood cells, liver and other tissue.[5)] Biological half-life is 4 to 12 hours.

(2) Molecular species of enzymes involved in metabolism (CYP450, etc.)

No applicable data

(3) Initial permeation effects and ratio, if any

No applicable data

(4) Metabolite action and ratio, if any

No applicable data

(5) Kinetic parameters of metabolites

No applicable data

6. Excretion

(1) Excretion site and route

There are excretions in the urine and excretions in bile in the form of trichloroethanol, glucuronic acid conjugate and trichloro acetic acid.

(2) Excretion rate

At 24 hours after administration, 17 to 40% is excreted in the urine comprising 4.6% (0.5 to 19%) of the dosage (15mg/kg) as an unaltered substance, combined with glucuronic acid conjugate.

(3) Excretion speed

Trichloro acetic acid excretion is slower with 10% or less during the first two hours, 25% or less during the next 6 hours and reaching 38% at 24 hours (excretion is slow and there are still traces in the blood even three days after administration).

7. Transporter Information

No applicable data

8. Extraction Ratio by Dialysis, etc.

No applicable data

Safety Matters (precautions in use)

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1. Warnings and Reasons

None

2. Contraindications and Reasons (including contraindications in principle)

Contraindications (do not administer to the following patients)

(1) Hypersensitivity to the active substance, to chloral hydrate [TRICLONAM is converted to trichloroethanol in the body the same way as chloral hydrate] or to any of the excipients listed in section Pharmaceutical Particulars.

(2) Patients with acute intermittent porphyria [TRICLONAM exacerbates the symptoms of porphyria]

3. Precautions Related to Indications or Effects and Reasons

None

4. Precautions and Related to Dosage and Administration and Reasons

None

5. Careful Administration Warnings and Reasons

Careful administration (extra care should be taken when administering to the following patients)

(1) Patients with hepatic disorder or renal disorder [TRICLONAM is hydrolyzed in the liver, converting it to trichloroethanol, then excreted by the kidneys, leading to risk in exacerbating adverse reactions in patients due to maintained and increased blood concentration]

(2) Children (see 11. Pediatric Use, etc.)

(3) Weak patients [may cause respiratory depression]

(4) Patients with reduced respiratory function [may cause respiratory depression]

(5) Patients with serious heart disease or arrhythmia [may exacerbated symptoms due to inhibited cardiac function]

(6) Elderly patients (See 9. Use in Elderly)

6. Important Precautions, Reasons and Measures

Important precautions

(1) Monitor patients carefully due to risk of respiratory depression. Especially in children, careful attention must be given to respiratory rate, heart rate, percutaneous arterial blood oxygen saturation, etc., through monitoring. (See 5. Careful Administration Warnings and Reasons, 8. Adverse Reactions (2) Serious Adverse reactions and Initial Symptoms, 11. Pediatric Use, etc.)

(2) As chloral hydrate is converted into the in vivo metabolite trichloroethanol, in the same way as TRICLONAM, combined use may cause overdosage. (See 13. Overdosage)

(3) Patients administered TRICLONAM must be warned not to engage in operating dangerous machinery, such as motor vehicles.

(4) Since prolonged administration may cause drug dependency, avoid long-term use through random, continued administration. Take careful consideration of therapeutic necessity when continuing administration. (See 8. Adverse reactions (2) Serious Adverse reactions and Initial Symptoms)

7. Drug Interactions

(1) Contraindications for coadministration and reasons

None

(2) Precautions for coadministration and reasons

[Precautions for Co-administration] (TRICLONAM should be administered with care when co-administered with the following drugs)

Drug name, etc.	Clinical symptoms and procedures	Mechanism and risk factors

Central nervous system depressants Phenothiazine derivative Barbiturates Monoamine oxidase inhibitors	TRICLONAM may exacerbate these effects, so take careful care if administration is unavoidable.	There is a possibility of enhanced central nervous system depressant action.
Alcohol		It competitively prohibits alcohol dehydrogenase, increasing blood concentration of alcohol.
Coumarin-based anticoagulants Warfarin, etc.	There is a possibility of exacerbating these effects, so in case of coadministration, carefully administer drug while measuring prothrombin levels more frequently than usual.	Trichloro acetic acid, a major metabolite, isolates and replaces warfarin from the blood plasma protein coupling site and increases free-type warfarin concentration.

8. Adverse Reactions

(1) Summary of adverse reactions

There has been no research, such as a treatment outcome study, to determine the incidence of occurrence of adverse reactions.

(2) Serious of adverse reactions and initial symptoms

Serious adverse reactions

1) Respiratory arrest, respiratory depression (incidence unknown): Respiratory arrest and respiratory depression may occur, and there are also reports of symptoms resulting in cardiopulmonary arrest, so respiratory conditions must be monitored carefully and appropriate measures taken in case of abnormality.

2) Shock, anaphylaxis, (incidence unknown): Shock and anaphylaxis may occur, so patient must be monitored carefully and in case pruritus, edema, respiratory distress, decreased blood pressure, cyanosis, etc. occur, discontinue administration and take appropriate measures.

3) Dependence (incidence unknown): Since prolonged administration may cause drug dependency, monitor patient carefully and take careful care in dosage and duration of administration. Furthermore, sudden dosage reduction or discontinuation after prolonged use may cause withdrawal symptoms such as convulsive seizure, delirium, tremors, anxiety, etc. In case of discontinuing administration, carefully reduce dosage gradually.

(3) Other adverse reactions

Other adverse reactions

In case any of the following adverse reactions occur, take appropriate measures based on symptoms.

	Frequency unknown
Hypersensitivity[Note)]	Rash, erythema, blister, fixed drug eruption, pruritus, fever
Circulatory system	Bradycardia
Liver	Increase in AST (GOT) and ALT (GPT)
Blood[Note)]	Eosinophilia, leukopenia
Digestive system	Nausea/vomiting, flatulence, stomachache
Neuropsychiatric	Headache, dizziness, lightheadedness, ataxia, erethism, depression, dysarthria, delayed awakening
Other	Edema, decreased urine volume, ketonuria

Note) In these cases, discontinue administration.

(4) List of adverse event frequency and abnormalities in clinical laboratory values by category

The incidence of adverse reactions in combination with tablets* was 202 cases (6.33%) out of 3,189 cases.

	Cases	Incidence (%)		Cases	Incidence (%)
Headache	11	0.34	Lack of restraint	1	0.03
Vomiting	3	0.09	Elation	1	0.03

Nausea	5	0.16	Hyperactivity	1	0.03
Abdominal pain	1	0.03	Fear	1	0.03
Gastric irritation	12	0.38	Nightmares	1	0.03
Stomach discomfort	1	0.03	Nervousness	1	0.03
Reflux	2	0.06	Insomnia	1	0.03
Heartburn	2	0.06	Incoordination	1	0.03
Flatulence	3	0.09	Ataxia	3	0.09
Mental desensitization	1	0.03	Sluggish movement	1	0.03
Fatigue/drowsiness	32	1.00	Hangover-like feeling	3	0.09
Dizziness, light-headedness	14	0.44	Residual action	9	0.28
Aftertaste	1	0.03			

* triclofos sodium tablets were taken off the market in 1975

(5) Incidence of adverse reactions by background, including underlying disease, complications, severity and whether or not surgery was performed

No applicable data

(6) Precautions and study methods for drug allergy

1) Patients with a history of hypersensitivity to the components of TRICLONAM or chloral hydrate.
2) Shock and anaphylaxis may occur as major adverse reactions, so patient must be monitored carefully and in case pruritus, edema, respiratory distress, decreased blood pressure, cyanosis, etc. occur, discontinue administration and take appropriate measures.
3) Rash, erythema, blister, fixed drug eruption, pruritus or fever may occur. If such symptoms occur, discontinue administration.

Reporting of suspected adverse reactions:
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

9. Use in the Elderly

TRICLONAM may cause respiratory depression in elderly patients. Since adverse reactions are likely to occur in general, administer drug carefully, for example by starting with minimal dosage.

10. Use during Pregnancy, Delivery or Lactation, etc.

Preferably, TRICLONAM should not be administered to pregnant women or woman who may be pregnant. [Safety in administration during pregnancy has not been established]

11. Pediatric Use, etc.

(1) In general, children have a higher drug sensitivity than adults, so administer drug carefully, for example by starting with minimal dosage (there have been many reports of respiratory arrest, respiratory depression and convulsions children with low birth weight, newborns, and infants)
(2) There are reports of respiratory arrest and respiratory depression occurring, leading to heart failure, so drug must be administered carefully and patient must be monitored closely. (See 6. Important Precautions, Reasons and Measures)
(3) Convulsions (clonic convulsions, partial attacks, etc.) may occur, so administer carefully.

12. Effects in clinical test results

No applicable data

13. Overdose

Signs and symptoms: Respiratory arrest, bradycardia and decreased blood pressure were found. (See 6. Important Precautions, Reasons and Measures)
Treatment: In the event of overdose, monitor respiration, pulse, blood pressure, percutaneous arterial blood oxygen saturation, and take appropriate measures, such as securing the airway. There have been reports that hemodialysis and blood perfusion are effective.

Acute overdose: Similar to symptoms of acute barbiturates poisoning. In addition, effects as a stimulant appear. The first symptom is vomiting followed by stomach necrosis that progresses to

stenosis. There have been reports of cardiac arrhythmias. Jaundice leads to liver disorder. Renal disorder is accompanied by Alb urine.
Chronic oral ingestion at high dose: Gastritis, skin rash, teleangiectasia, hypotension, reduced myocardial function, renal disorder.
Sudden discontinuation of drug causes withdrawal symptoms such as tremors and delirium.
Treatment: Administer palliatives such as liquid paraffin, in order to relieve stomach and esophageal irritation. Administer lidocaine hydrochloride (xylocaine) to manage heart arrhythmia. Forced diuresis or dialysis are effective for severe toxicity.

14. Precautions in Application

None

15. Other Precautions

None

16. Excipients

This medicinal product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains 50 mg sodium per 5ml, equivalent to 2.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Matters Related to Non-clinical Studies

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1. Pharmacological Studies

(1) Pharmacological studies (see Pharmacology Matters)

(2) Secondary pharmacology studies

No applicable data

(3) Safety pharmacology studies

No applicable data

(4) Other pharmacological studies

No applicable data

2. Toxicity Studies

(1) Single dose toxicity studies

Acute toxicity[6)]

Mouse (♀) Orally LD_{50} 1470mg/kg
Rat (♀) Orally LD_{50} approx. 1900mg/kg

(2) Repeated dose toxicity studies

Subacute toxicity, chronic toxicity[6,9,10)]

There were abnormal findings in subacute toxicity and chronic toxicity studies in which male and female PVG rats were fed a diet supplemented with 0.03%, 0.1% and 0.3% W/W triclofos sodium, and the control group was fed a normal diet. In addition, there were no findings considered to be attributable to triclofos sodium in death rate, incidence of interval illness, growth rate, organ weight, histological findings, hematological findings or blood biochemical findings. Furthermore, in the results of oral administration of 67 to 100 mg/kg disodium trichlorethyl phosphate to WAG rats for 30 days, no abnormal changes were found in any major organs, there was no delayed growth, stomach irritation or damage to heart, liver or kidneys.

Table: Abnormal Findings in Study of Subacute and Chronic Toxicity in PVG Rats

Test Days	Organ weight	Histological findings	Hematological findings	Biochemical findings
28	Adrenal gland hypertrophy Liver and kidney hypertrophy	(Testicles) Many abnormal sperm cells were found in one subject, but cells were normal in other rats and in this rat during other periods.		
84	Same as above	(Thyroid gland) One female presented with a swollen thymocyte tissue nodule.	ERYTHROPOIESIS may have been	Male, Reduced serum

		(Adrenal gland) There were more lipids in the males than in females, but there were no differences from the control group.	caused to males in the 0.3%W/W group.	inorganic phosphorus

Test Days	Organ weight	Histological findings	Hematological findings	Biochemical findings
168	Same as above		Same as above Male, Slight increase in blood urea, but the value was within normal range.	Same as above Male, Increased serum calcium
364	Same as above			Male, Slightly decreased serum calcium Male/female, Slightly increased serum calcium
728	Possible effects of hypertrophy of liver and kidney, and increased pituitary weight in males.			Male, decreased serum bilirubin

(Note) Blank columns indicate no apparent abnormalities.

(3) Reproductive and developmental toxicity studies

Rabbits were orally administered 300 mg/kg/day of triclofos sodium, but no abnormalities occurred in the infant rabbits. The number of fetuses were the same as the control group.

(4) Other special toxicity

No applicable data

Pharmaceutical Particulars

1 List of excipients

Sucrose, Ethanol 95%, Sodium Hydroxide, Orange Oil 926, Lemon Oil NO, Vanillaroma 200, Saccharin Sodium, Nipastat, Disodium Edetate, Hydrochloride acid 37%, Sodium Carbonate anhydrous, Sunset Yellow, Purified Water

2 Incompatibilities

Not applicable.

3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after first opening: 110 days

4 Special precautions for storage

Store below 25°C

5 Nature and contents of container

100 ml of syrup in an amber transparent glass bottle (type III) with a child proof cap, tamper evident in a carton box.

6 Special precautions for disposal and other handling

No special requirements.

Marketing Authorisation Holder and Manufacturer

CTS CHEMICAL INDUSTRIES LTD
POB 385,KIRYAT-MALACHI,ISRAEL

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