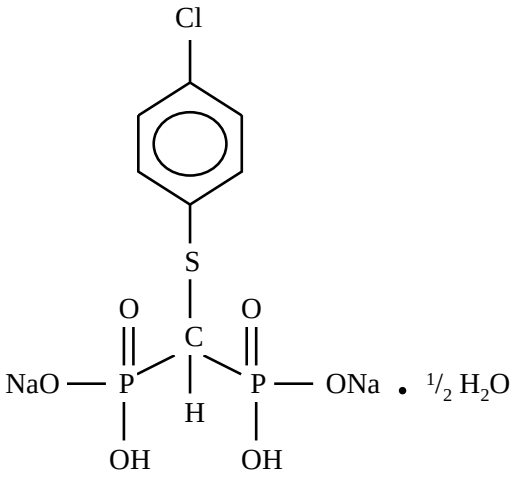
PRODUCT INFORMATION

SKELID

NAME OF THE MEDICINE

Tiludronate Disodium

CHEMICAL STRUCTURE



CAS No: 149845-07-8

DESCRIPTION

Skelid (Tiludronate Disodium) is designated chemically as [[(p-chlorophenyl) thio] methylene] bisphosphonic acid, disodium salt, hemihydrate.

Tiludronate disodium is a practically white powder, freely soluble in water with a molecular weight of 371.6 and an empirical formula $C_7H_7ClNa_2O_6P_2S$**.** $\frac{1}{2}H_2O$. Each tablet contains 200 mg tiludronic acid as tiludronate disodium and the excipients; lactose, sodium lauryl sulfate, crospovidone, hypromellose and magnesium stearate.

PHARMACOLOGY

PHARMACODYNAMICS

Skelid reduces bone turnover and acts primarily as an antiosteoclastic medicine. It has an inhibitory effect on bone resorption at dose levels which do not depress bone formation, particularly mineralisation. In Paget's disease of the bone, the transient maintenance of a normal bone formation rate in the presence of inhibition of the resorptive process leads to an increase in bone mass which is associated with a positive calcium balance. Reduced bone turnover is often accompanied by symptomatic improvement including a reduction in bone pain.

PHARMACOKINETICS

Approximately 6%-8% of an orally administered dose of Skelid (400 mg/day) is absorbed. Maximum plasma concentrations are observed 1 to 2 hours after dosing. There is a wide inter and intra-individual variability in the extent of absorption. Following chronic administration in patients plasma levels of tiludronic acid were between 1 and 5 mg/L. Plasma protein binding was 91% over a range of concentrations.

Approximately half of the absorbed dose is bound to bone. 40 to 50% of an orally administered dose remains in the bone beyond 13 days. Skelid is excreted unchanged in urine. Elimination half-life is dependent on release from bone, a slow process probably linked to bone remodelling.

A randomised study was conducted to assess the effect of food on tiludronate absorption after administration of 400 mg of tiludronate to 10 subjects as a single dose. In the subjects administered tiludronate with food a large decrease in Cmax (0.42 mg/L versus 1.99 mg/L) and AUC (2.12 mg/h/L versus 19.38 mg/h/L) was observed compared to the fasted subjects. This corresponded to a 80-90% decrease in bioavailability.

CLINICAL TRIALS

The safety and efficacy of tiludronate in Paget's disease of the bone was examined in 4 pivotal trials (3 placebo- controlled studies and one etidronate-controlled study enrolling 633 patients) and some supportive trials involving 1167 patients with Paget's disease. Of the patients enrolled in the pivotal trials, 183 were treated with the recommended regimen of tiludronate ie 400mg per day for 3 months.

The principal criterion to assess efficacy in these trials was serum alkaline phosphatase. Other criteria used were urinary hydroxyproline and the pagetic pain scores.

In the placebo-controlled studies, at 3 months and 6 months, a statistically significant decrease of serum alkaline phosphatase levels was seen in the tiludronate 400 mg/day group when compared with placebo. Pain improvement was not significantly better compared to placebo.

The incidence of treatment success in these studies (defined as the proportion of patients demonstrating at least 50% reduction of serum alkaline phosphatase at 3 months) was 55-60% for the tiludronate patients on 400 mg/day.

In the etidronate-controlled study, at 3 months and 6 months, a statistically significant decrease in the levels of serum alkaline phosphatase was seen in the tiludronate 400 mg/day patients when compared to etidronate 400 mg/day patients.

In this study , the incidence of treatment success (defined by $\geq$ 50% reduction in serum alkaline phosphatase) in the tiludronate patients on 400 mg/day was 55% at 3 months and 60% at 6 months compared with the etidronate treatment group where treatment success was 14% at 3 months and 25% at 6 months. No significant difference between treatments was found in terms of urinary hydroxyproline levels or bone pain.

In the long term studies, the time between treatment courses reached 18 months on average for the first course and 12 months during the second course of treatment. The change in median adjusted serum alkaline phosphatase was significantly different from baseline in each course of the study and did not differ between successive courses. The nadir median adjusted serum alkaline phosphatase reached was 30 to 50% above the upper limit of the normal range.

The dose of the medicine in the above studies was given at various times in relation to feeding, mostly 2 hours apart from meals. Overall, 400 mg per day of tiludronate given for 3 to 6 months had a significant effect in lowering serum alkaline phosphatase in Pagetic patients for up to 18 months.

As with other bisphosphonates, the most frequent adverse effects reported in the studies were gastrointestinal in nature, with no cases of oesophagitis. The overall incidence of fractures was 1.4% patients years.

INDICATIONS

Skelid is indicated in the treatment of Paget's disease of bone.

CONTRAINDICATIONS

Skelid should not be given to patients with a history of allergic reactions to bisphosphonates.

Skelid should not be given to patients who are hypersensitive to any of the other ingredients in the tablets.

Skelid should not be used in Juvenile Pagetic patients as safety and efficacy has not been established.

PRECAUTIONS

Skelid is excreted unchanged via the kidney. Though no related adverse experiences have been reported in clinical trials, caution should be exercised in patients with mild to moderate renal failure.

Skelid is not recommended in patients with severe renal failure (creatinine clearance less than 30 mL/min). Skelid should be administered with caution (e.g. regular monitoring of the renal function) in cases of mild renal failure (creatinine clearance between 60 and 90 mL/min) and moderate renal failure (creatinine clearance between 30 and 60 mL/min).

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates (Refer to Adverse Effects). Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop Osteonecrosis of the jaw while on bisphosphonates therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonates treatment reduces the risk of Osteonecrosis of the jaw.

Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of the external auditory canal have been reported with bisphosphonate therapy.

In post marketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent. This category of medicines includes Skelid tablets. The time to onset of symptoms varied from one day to several months after starting the medicine. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same medicine or another bisphosphonates (Refer to Adverse Effects).

Bisphosphonates have been associated with oesophagitis, gastritis, oesophageal ulcerations and gastroduodenal ulcerations. Thus caution should be used

- In patients with a history of oesophageal disorders which delay oesophageal transit or emptying eg stricture or achalasia.
- In patients who are unable to stay in the upright position for at least 30 minutes after taking the tablet.
- In patients with active or recent oesophageal or upper gastrointestinal problems.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

Patients should maintain an adequate intake of calcium and vitamin D: calcium metabolism disorders (hypocalcaemia, vitamin D deficiency) should be corrected before initiating treatment.
Patients should not suck or chew Skelid tablets because of the potential for developing stomatitis and/or oropharyngeal ulceration (see Dosage and Administration).

EFFECTS ON FERTILITY

Treatment of male and female rats with an oral tiludronate dose of 75 mg/kg/day tiludronate showed no adverse effect on male and female fertility, however, the exposure to tiludronate in these studies would have been less than human exposure at the maximum recommended clinical dose based on AUC.

USE IN PREGNANCY (CATEGORY B2[1])

Tiludronate may through its pharmacological effects on calcium homeostasis be hazardous to the fetus and/or newborn child. Reproduction studies in mice, rats and rabbits using the oral route of administration showed no evidence of teratogenicity or fetotoxicity due to tiludronate (available pharmacokinetic data suggest that the doses used in the rat study may have resulted in exposure levels greater than human exposure at the maximum recommended clinical dose, based on plasma concentrations).

Post natal survival of rats was not affected at oral doses up to 75 mg/kg/day, however, the exposure to tiludronate in this study would have been less than human exposure at the maximum recommended clinical dose, based on AUC. There are no adequate or well controlled trials of tiludronate in pregnant women. Tiludronate should not be used during pregnancy unless absolutely necessary.

[1] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

USE IN LACTATION

There is no clinical experience with tiludronate in lactating women and it is not known whether it passes into breast milk. There have been no animal studies investigating the passage of tiludronate into the milk. Breastfeeding is, therefore, not recommended during treatment with skelid.

PAEDIATRIC USE

Skelid is not indicated in juvenile Paget's disease of bone.

GENOTOXICITY

Tiludronate was inactive in genotoxicity tests for gene mutations, clastogenicity and DNA damage.

CARCINOGENICITY

Oral tiludronate did not show any oncogenic activity in long term animal studies (mouse and rat). Investigations of exposure to the medicine in these studies were limited to plasma concentrations at two hours post dose. Based on this parameter, maximum exposure in the rat study was approximately 0.3 (female rats) and 0.6 (male rats) times the human exposure at the maximum recommended clinical dose. Exposure in the mouse study was approximately 0.02 times the human exposure at the maximum recommended clinical dose.

INTERACTIONS WITH OTHER MEDICINES

The pharmacokinetic parameters of Skelid are not significantly altered by the co-administration of aspirin or diclofenac.

The pharmacokinetic parameters of digoxin are not significantly altered by concomitant treatment with Skelid.

The bioavailability of tiludronic acid is increased with concomitant administration of indomethacin.

Because calcium decreases the absorption of tiludronate disodium, it should not be taken within 2 hours (before and after) of antacids containing calcium, aluminium and magnesium hydroxide, mineral supplements, calcium supplements or food with a high calcium content.

ADVERSE EFFECTS

Very common ≥10%; Common ≥1 and <10%; Uncommon ≥0.1 and <1%; Rare ≥0.01 and <0.1%; Very rare <0.01%; Not known

Most of the reported adverse events have been mild to moderate and have not required drug discontinuation and/or corrective medication.

Adverse events with Skelid are mainly of gastro-intestinal origin. Common side effects include abdominal pain, nausea and diarrhoea.

In the clinical trials, the incidence of these events was dose related.

Gastrointestinal inflammation including oesophagitis and gastric ulceration have been reported but their frequency is not known.

Uncommon reports of rash have been reported.

Rarely cases of asthenia, dizziness, vertigo, headache and skin reaction have also been reported.

Adverse events reported in three pivotal clinical trials of tiludronate with placebo or etidronate are tabulated below:

Number and Rate of Adverse Events (Reported by at least 5% of patients in any treatment group) in the three tiludronate pivotal trials (two placebo and one etidronate controlled).

Adverse Event	**Tiludronate Double Blind Controlled Studies with either placebo or etidronate)**		
	Placebo n=74 (Studies P1845 & P1619)	**Tiludronate (400mg/day) (n=153) (Studies P1845, P1619, P1552)**	**Etidronate (400mg/day) (n=79) (Study P1552)**
Gastro-intestinal system	19 (25)	40 (26)	10 (13)
Nausea	4 (5)	9 (6)	2 (3)
Dyspepsia	6 (8)	6 (4)	2 (3)
Abdominal pain	3 (4)	11 (8)	2 (3)
Body as a whole, general disorders	26 (35)	30 (20)	6 (8)
Pain	17 (23)	17 (11)	2 (3)
Back Pain	6 (8)	7 (4)	2 (3)
Influenza-like symptoms	4 (5)	3 (2)	1 (1)
Central & Peripheral nervous system. (including dizziness, headaches)	14 (19)	19 (12)	1 (1)
Musculo-skeletal system (any)	14 (19)	14 (9)	7 (9)
Arthralgia	4 (5)	3 (2)	1 (1)
Skeletal Pain	6 (8)	2 (1)	-
Psychiatric	7 (9)	2 (1)	2 (3)
Skin & Appendages	8 (11)	12 (8)	3 (4)
Respiratory System (including rhinitis)	19 (26)	20 (13)	5 (6)
Metabolic & Nutritional	5 (7)	9 (6)	1 (1)
Urinary system	9 (12)	1 (0)	-

() = % of patients per group

Musculoskeletal: bone, joint, and/or muscle pain, rarely severe and/or incapacitating (Refer to **Precautions**).

POST-MARKETING

Injury, Poisoning and Procedural complicatons: atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including tiludronate (bisphosphonate class adverse reaction).

DOSAGE AND ADMINISTRATION

Skelid should be taken as a single oral dose, as detailed below, with a glass of water, at least 2 hours before or after a meal. Patients should be advised not to eat at least 2 hours before and after dosing, particularly milk, milk products or foods with a high calcium content nor should they take antacids containing calcium, aluminium or magnesium within this period. Patients should not lie down for 30 minutes after taking the tablet.

Patients should not suck or chew Skelid tablets because of the potential for developing stomatitis and/or oropharyngeal ulceration (see Precautions).

ADULTS/ELDERLY

Skelid should be given as a total single daily dose of 400 mg (2 tablets) for 3 months. Most patients respond to therapy within a 3 month treatment period whether or not they have been previously treated with another bisphosphonate.

The improvement observed may continue for 18 months after the therapy has ceased.

The treatment course may be repeated at the discretion of the physician based on clinical observation, pain and recurrence of elevated serum phosphatase levels. (Refer to **PHARMACOLOGY-Clinical Trials**).

CHILDREN

Skelid is not indicated in juvenile Paget's disease of bone.

OVERDOSAGE

No experience with Skelid tablets is available. However, following a substantial overdose, hypocalcaemia and acute renal failure might be expected in some patients. Gastric lavage may remove unabsorbed medicine and symptomatic procedures for the treatment of hypocalcaemia and/or renal failure should be used.

In case of overdose, immediately contact the Poisons Information Centre for advice (In Australia 13 11 26. In New Zealand, call 0800 764 766.)

PRESENTATION AND STORAGE CONDITIONS

200 mg tablets: 56's

Store below 30^{o}C.

NAME AND ADDRESS OF THE SPONSOR

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

07 February 1997

DATE OF MOST RECENT AMENDMENT

26 February 2016

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