# Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion

(Disodium clodronate tetrahydrate)

PL 22191/0001

**UKP AR**

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Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion

(Disodium clodronate tetrahydrate)

PL 22191/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Sindan Limited a Marketing Authorisation (licence) for the medicinal product Disodium clodronate 60mg/ml Concentrate for Solution for Infusion (PL 22191/0001) on 23rd September 2009. This is a prescription-only medicine (POM).

Disodium Clodronate belongs to a group of medicines called bisphosphonates which help prevent the loss of calcium from bones, particularly associated with cancer. Disodium Clodronate can reduce abnormally high levels of calcium in your blood.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Disodium clodronate 60mg/ml Concentrate for Solution for Infusion outweigh the risk, hence a Marketing Authorisation has been granted.
Disodium clodronate 60 mg/ml Concentrate
for Solution for Infusion

(Disodium clodronate tetrahydrate)

PL 22191/0001

SCIENTIFIC DISCUSSION

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**INTRODUCTION**

Based on the review of the data on quality, safety and efficacy, the MHRA granted Sindan Limited a Marketing Authorisation (licence) for the medicinal product Disodium clodronate 60mg/ml Concentrate for Solution for Infusion (PL 22191/0001) on 23rd September 2009. The product is a prescription-only medicine (POM) indicated for the treatment of hypercalcaemia of malignancy.

The application was submitted as a national, abridged application, according to Article 10.1 of Directive 2001/83/EC, as amended. The applications refer to the UK originator product, Bonefos 60mg/ml Concentrate for I.V. Injection (PL 00015/0134), authorised to Boehringer Ingelheim Limited on 5th April 1991.

The active substance, disodium clodronate is a bisphosphonate (formerly diphosphonates), a group of analogues of pyrophosphate, which have been shown, *in vitro*, to inhibit the formation and dissolution of calcium phosphate (hydroxyapatite). *In vivo*, they have been shown to inhibit bone resorption to a greater or lesser extent, depending on the compound, and disodium clodronate is one of the most effective in this respect.

The drug product is presented as a colourless to pale yellow concentrate for solution for infusion. It is diluted in either 0.9 % sodium chloride solution or 5% glucose solution to give the solution for infusion.

Disodium clodronate is eliminated mainly via the kidneys, and after intravenous doses, 60-80% will be found in urine within 48 hours. Distribution studies in animals suggest that the remainder is retained in bone tissue. Total systemic clearance is, on average, 110 ml/min and the renal clearance 90 ml/min. Disodium clodronate is not metabolised. The half-life for elimination from plasma is 2 hours but a second phase with a half life of 13 hours has been identified although less than 10% of total urinary excretion takes place during this phase. The substance, which is bound to bone will be excreted more slowly at a rate corresponding to bone turnover. The binding of disodium clodronate to serum proteins is low. The kinetics of disodium clodronate are linear after both intravenous infusion and oral doses.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Sodium clodronate

Nomenclature:

INN: Sodium clodronate

Chemical names:

i) (Dichloromethylene) diphosphonic acid sodium salt, tetrahydrate

ii) (Phosphonic acid, (dichloromethylene) bis-, disodium salt, tetrahydrate

Structure:

\[
\begin{align*}
&\text{O}^+\text{Na}^+ \\
&\text{O}=\text{P} \text{OH} \\
&\text{Cl} \text{C} \text{Cl} , 4\text{H}_2\text{O} \\
&\text{O} \text{P} \text{OH} \\
&\text{O}^+\text{Na}^+
\end{align*}
\]

Molecular formula: \(\text{CH}_2\text{Cl}_2\text{Na}_2\text{O}_6\text{P}_2 \ , 4\text{H}_2\text{O}\)

Molecular weight: 360.93 (anhydrous: 288.9)

CAS No: 22560-50-5

Physical form: A white crystalline powder

Solubility: Freely soluble in water, practically insoluble in ethyl ether, chloroform, and benzene

The active substance, sodium clodronate, is the subject of a European Pharmacopeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

An appropriate active substance specification has been provided. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.
The active substance is stored in appropriate packaging. It is packed into an inner polyethylene bag, within a sealed polyethylene/aluminium bag, contained in a fibrite keg. Specifications and Certificates of Analysis for all packaging components used have been provided. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a shelf-life of 5 years with a retest period of 18 months, when stored in the proposed packaging.

**DRUG PRODUCT**

**Description & Composition**

The drug product is presented in glass vials as a colourless to pale yellow concentrate for solution for infusion, which is diluted before use.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride (for pH adjustment) and water for injections. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used.

A manufacturing overage is not warranted. The applicant includes a filling overage of 6% to ensure the extraction of volume declared by the label is met, which is acceptable.

**Impurity profiles**

Comparative impurity data were provided for the test and suitable reference products. The impurity profiles were found to be similar, with all impurities within the specification limits.

**Pharmaceutical development**

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.
Finished product specification

The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided for three commercial scale batches and they comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The drug product is packed in Type I transparent, colourless, glass vials of size 5ml, containing 300mg disodium clodronate in a 60mg/ml strength solution. The vials are sealed with bromobutyl rubber / silicate filler stoppers and aluminium caps with polypropylene disks. The vials are packaged individually, with the product information leaflet, in cardboard outer cartons.

Specifications and Certificates of Analysis for all packaging components used have been provided, and are satisfactory. All primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral preparations.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set, with storage instructions ‘Store in the original package.’. This is satisfactory. For details of in-use storage time and storage conditions of the diluted medicinal product, please refer to the SmPC.

Bioequivalence Study

A bioequivalence study is not necessary to support this application for a parenteral product.

EXPERT REPORT

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:

The approved SmPC, leaflet, and labelling are satisfactory. Colour mock-ups of the labelling and PIL have been provided.

Conclusion

The proposed product, Disodium clodronate 60mg/ml Concentrate for Solution for Infusion, has been shown to be a generic version of the reference product, Bonefos 60mg/ml Concentrate for I.V. Injection (PL 00015/0134, Boehringer Ingelheim Limited), with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product, which has been licensed in the UK for over 10 years. Given the
route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. A Marketing Authorisation has therefore been granted.
**PRECLINICAL ASSESSMENT**

The application was submitted as a national, abridged, application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for applications of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory. An appropriate CV for the expert has been supplied.
CLINICAL ASSESSMENT

INDICATIONS
Disodium clodronate 60mg/ml Concentrate for Solution for Infusion is indicated in the treatment of hypercalcaemia of malignancy.

The indication is consistent with that for the UK reference product and is satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION
Please refer to SmPC for details. The posology is consistent with that for the UK reference product and is satisfactory.

TOXICOLOGY
No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY
No new data are submitted and none are required for this type of application.

Pharmacodynamics
Disodium clodronate belongs to the group of drugs known as bisphosphonates (ATC Code M05B A02). Bisphosphonates (formerly diphosphonates) are a group of analogues of pyrophosphate, which have been shown, in vitro, to inhibit the formation and dissolution of calcium phosphate (hydroxyapatite). In vivo, they have been shown to inhibit bone resorption to a greater or lesser extent, depending on the compound, and disodium clodronate is one of the most effective in this respect.

Pharmacokinetics
Disodium clodronate is eliminated mainly via the kidneys, and after intravenous doses, 60-80% will be found in urine within 48 hours. Distribution studies in animals suggest that the remainder is retained in bone tissue. Total systemic clearance is, on average, 110 ml/min and the renal clearance 90 ml/min. Disodium clodronate is not metabolised. The half-life for elimination from plasma is 2 hours but a second phase with a half life of 13 hours has been identified although less than 10% of total urinary excretion takes place during this phase. The substance, which is bound to bone will be excreted more slowly at a rate corresponding to bone turnover. The binding of disodium clodronate to serum proteins is low. Due to low uptake from gastrointestinal tract, the bioavailability of oral doses is 1-4%. The kinetics of disodium clodronate are linear after both intravenous infusion and oral doses.

EFFICACY
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of sodium clodronate is well-established from its extensive use in clinical practice.

Disodium clodronate 60mg/ml Concentrate for Solution for Infusion is to be administered as an aqueous intravenous solution and contains the same active substance, in the same concentration, as the UK reference product Bonefos 60mg/ml Concentrate for I.V. Injection. Thus, in accordance with the “Note for Guidance on
the Investigation of Bioavailability and Bioequivalence”, (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

SAFETY
No new data are submitted and none are required for this type of application. No new or unexpected safety concerns arose from this application. Safety is reviewed in the clinical overview. The safety profile of sodium clodronate is well-known.

EXPERT REPORT
The expert overview on the clinical aspect of the product proposed for marketing was satisfactory. The clinical overview contains a sufficient outline of the published literature concerning the clinical pharmacology, efficacy and safety of sodium clodronate. The report was prepared by an appropriately qualified expert for whom a satisfactory CV has been supplied.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is consistent with that for the reference product and is acceptable.

Patient Information Leaflet (PIL)
The final PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

CONCLUSION
The grounds for establishing the proposed product as a generic version of the reference product, Bonefos 60mg/ml Concentrate for I.V. Injection (PL 00015/0134), are considered adequate. The product literature is approved.

Sufficient clinical information has been submitted to support this application. When used as indicated, Disodium clodronate 60mg/ml Concentrate for Solution for Infusion has a favourable benefit-to-risk ratio. Therefore, the grant of a Marketing Authorisation was recommended on medical grounds.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Disodium clodronate 60mg/ml Concentrate for Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s Disodium clodronate 60mg/ml Concentrate for Solution for Infusion (PL 22191/0001) has been demonstrated to be a generic version of the reference product, Bonefos 60mg/ml Concentrate for I.V. Injection (PL 00015/0134, Boehringer Ingelheim Limited).

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that patients/users are able to act upon the information that the leaflet contains.

Colour mock-ups of the labelling have been provided. The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s product and the UK reference product are interchangeable. Extensive clinical experience with sodium clodronate is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.
Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion

(Disodium clodronate tetrahydrate)

PL 22191/0001

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 1st December 2004
2. Following standard checks and communication with the applicant the MHRA considered the applications valid on 8th December 2004
3. Following assessment of the applications the MHRA requested further information relating to the quality dossier on 12th June 2006
4. The applicant responded to the MHRA’s request, providing further information for the quality sections on 22nd January 2007
5. Following assessment of the responses the MHRA requested further information relating to the quality sections on 17th October 2007
6. The applicant responded to the MHRA’s request, providing further information on for the quality sections on 31st March 2008
7. The application was determined on 23rd September 2009
SUMMARY OF PRODUCT CHARACTERISTICS
The UK Summary of Product Characteristics (SmPC) for Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Disodium Clodronate 60 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml vial contains 300 mg disodium clodronate (as the tetrahydrate) (60 mg/ml disodium clodronate).
For excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
The treatment of hypercalcaemia of malignancy.

4.2 Posology and method of administration
Patients must be kept adequately hydrated before, during and after the administration of Disodium Clodronate 60 mg/ml concentrate for solution for infusion.

Adults:
Disodium Clodronate 60 mg/ml concentrate for solution for infusion may be administered to adults as follows:

Single Infusion:
1500 mg (five 5 ml vials) Disodium Clodronate 60 mg/ml concentrate for solution for infusion in 500 ml of either 0.9% w/v saline or 5% glucose solution administered as an intravenous infusion over a period of four hours. Serum calcium levels should start to decrease 24 - 48 hours after the infusion.

Multiple Infusions:
As an alternative, 300 mg (one 5 ml vial) Disodium Clodronate 60 mg/ml concentrate for solution for infusion in 500 ml of either 0.9% Sodium Chloride Intravenous Infusion or 5% Glucose Intravenous Infusion administered as an intravenous infusion over a period of at least two hours on successive days until normocalcaemia is achieved or to a maximum of 7 days.

Response:
Whichever method of infusion is employed, most patients will achieve normocalcaemia within 5 days. For those who do not achieve a clinically acceptable serum calcium level, the infusion with Disodium Clodronate 60 mg/ml concentrate for solution for infusion may be repeated.

Further Treatment:
The length of time that a clinically acceptable serum calcium level is maintained after infusion of Disodium Clodronate 60 mg/ml concentrate for solution for infusion varies considerably from patient to patient. The infusion can be repeated as necessary to control the serum calcium level.
Renal function and serum calcium levels should be monitored during therapy. Dose reduction is recommended if deterioration in renal function becomes apparent (see below). Treatment
should be stopped if hypocalcaemia develops, and serum calcium levels monitored to determine whether further treatment is required.

**Renal impairment:**

There are no published data at present on which to base recommendations for dose reduction in renal impairment when considering the option of a single 1500 mg infusion in hypercalcaemia.

The dose of disodium clodronate should be reduced in renal impairment according to creatinine clearance when using divided intravenous doses of 300 mg. Thus in mild renal impairment with creatinine clearance of 50 - 80 ml/minute a 25% reduction in dose is recommended, in moderate renal impairment (10 - 50 ml/minute) a 25 - 50% reduction in dose is recommended. Disodium clodronate is contraindicated in patients with creatinine clearance below 10 ml/minute.

**Children:**

Disodium Clodronate has not been evaluated in children.

**Elderly:**

There are no special dosage recommendations in the elderly. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

4.3 **Contraindications**

Disodium Clodronate 60 mg/ml concentrate for solution for infusion is contraindicated in patients with known hypersensitivity to bisphosphonates, in patients with moderate to severe renal failure (serum creatinine greater than 440 micromol/l or creatinine clearance below 10 ml/minute), in children, in pregnant and lactating women, and in patients receiving other bisphosphonates.

4.4 **Special warnings and precautions for use**

Disodium Clodronate 60 mg/ml concentrate for solution for infusion should be administered with care to patients with renal insufficiency. It is recommended that appropriate monitoring of renal function with serum creatinine measurement be carried out during treatment.

4.5 **Interaction with other medicinal products and other forms of interaction**

Patients receiving NSAIDs in addition to disodium clodronate have developed renal dysfunction. However, a synergistic action has not been established. As aminoglycosides can cause hypocalcaemia concomitant disodium clodronate should be administered with caution. There is no evidence from clinical experience that disodium clodronate interacts with other medication such as steroids, diuretics, analgesics or chemotherapeutic agents.

4.6 **Pregnancy and lactation**

There are insufficient data either from animal or human studies on the effects of disodium clodronate on the foetus and on reproduction. No studies have been conducted on secretion in breast milk. Disodium Clodronate 60 mg/ml concentrate for solution for infusion is, therefore, contraindicated in pregnancy and lactation and should not be given to women of childbearing age unless they are taking adequate contraceptive precautions. Disodium clodronate is likely to adversely affect bone formation both in the foetus and in young children.

4.7 **Effects on ability to drive and use machines**

There is no indication to suggest any effects of Disodium Clodronate 60 mg/ml concentrate for solution for infusion on a patient's ability to drive or use machinery.
4.8 Undesirable effects

Hypersensitivity reactions have been mainly confined to the skin: pruritus, urticaria, and exfoliative dermatitis. Bronchospasm has been precipitated rarely in patients with and without a previous history of asthma. Renal dysfunction, including failure, has been reported.

Transient proteinuria has been noted immediately after intravenous infusion.

Reversible elevations of serum creatinine, parathyroid hormone, lactic acid dehydrogenase, transaminase and alkaline phosphatase have been reported. Asymptomatic hypocalcaemia has been noted infrequently; symptomatic hypocalcaemia is rare.

4.9 Overdose

No reports of overt poisoning with disodium clodronate have been received. It is theoretically possible that hypocalcaemia may develop up to 2 or 3 days following the overdose. Serum calcium should be monitored and oral or parenteral calcium supplementation may be needed.

No reports of overt poisoning with clodronate have been received.

One patient developed fatal renal failure after receiving extremely high doses of intravenous disodium clodronate. Transient increases in serum creatinine have been observed in two studies, suggesting that overdosage of intravenous disodium clodronate may lead to reduced renal function.

It is theoretically possible that hypocalcaemia may develop up to 2 or 3 days following the overdose. Serum calcium should be monitored and oral or parenteral calcium supplementation may be needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC: M05B A02

Disodium clodronate is a bisphosphonate (formerly diphosphonates), a group of analogues of pyrophosphate, which have been shown, in vitro, to inhibit the formation and dissolution of calcium phosphate (hydroxyapatite). In vivo, they have been shown to inhibit bone resorption to a greater or lesser extent, depending on the compound, and disodium clodronate is one of the most effective in this respect.

5.2 Pharmacokinetic properties

Disodium clodronate is eliminated mainly via the kidneys, and after intravenous doses, 60-80% will be found in urine within 48 hours. Distribution studies in animals suggest that the remainder is retained in bone tissue. Total systemic clearance is, on average, 110 ml/min and the renal clearance 90 ml/min. Disodium clodronate is not metabolised. The half-life for elimination from plasma is 2 hours but a second phase with a half life of 13 hours has been identified although less than 10% of total urinary excretion takes place during this phase. The substance, which is bound to bone will be excreted more slowly at a rate corresponding to bone turnover. The binding of disodium clodronate to serum proteins is low. Due to low uptake from gastrointestinal tract, the bioavailability of oral doses is 1-4%. The kinetics of disodium clodronate are linear after both intravenous infusion and oral doses.

5.3 Preclinical safety data

No further information relevant to clinical practice is available from preclinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide (for pH adjustment).

Water for Injections
6.2 Incompatibilities
None stated.

6.3 Shelf life
The shelf life expiry date for this product shall not exceed 24 months from the date of its manufacture.

6.4 Special precautions for storage
Store in the original package.

Solution in the original vial
This medicinal product does not require any special storage conditions.

Diluted solution
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container
Disodium Clodronate 60 mg/ml concentrate for solution for infusion is available in 5 ml colourless vials of Type I glass, packed into cartons containing 1 vial. The polypropylene disk in the metal capped is yellow.

6.6 Special precautions for disposal
For multiple infusions one 5 ml vial of Disodium Clodronate 60 mg/ml concentrate for solution for infusion is diluted in 500 ml of either 0.9% Sodium Chloride Intravenous Infusion or 5% Glucose Intravenous Infusion.

For single infusion five 5 ml vials of Disodium Clodronate 60 mg/ml concentrate for solution for infusion are diluted in 500 ml of either 0.9% Sodium Chloride Intravenous Infusion or 5% Glucose Intravenous Infusion.

7 MARKETING AUTHORISATION HOLDER
SINDAN Ltd.
81/8 Shepherds Hill
London N6 5RG
United Kingdom
Tel: +44(0)208 348 7759

8 MARKETING AUTHORISATION NUMBER(S)
PL 22191/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/09/2009

10 DATE OF REVISION OF THE TEXT
23/09/2009
PATIENT INFORMATION LEAFLET

Disodium Clodronate 60 mg/ml concentrated for solution for infusion

Disodium Clodronate

Read all of this leaflet carefully, before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Disodium Clodronate is and what it is used for
2. Before you use Disodium Clodronate
3. How to use Disodium Clodronate
4. Possible side effects
5. How to store Disodium Clodronate
6. Further information

1. WHAT DISODIUM CLODRONATE IS AND WHAT IT IS USED FOR

Disodium Clodronate belongs to a group of medicines called bisphosphonates which help prevent the loss of calcium from bones particularly associated with cancer. Disodium Clodronate can reduce abnormally high levels of calcium in your blood.

Disodium Clodronate is available as vials containing 300 mg disodium clodronate in a 60 mg/ml solution which has to be diluted before being given to you. The other ingredients are sodium hydroxide and water for injections.

1. BEFORE YOU USE DISODIUM CLODRONATE

Do not take Disodium Clodronate if:

- you are allergic (hypersensitive) to disodium clodronate or any of the other ingredients of Disodium Clodronate
- you have had an allergic reaction (causing rash, itching, or more rarely shortness of breath) to Disodium Clodronate or to similar medicines
- you are a patient with moderate to severe renal (kidney) failure (serum creatinine greater than 440 micromol/l or creatinine clearance below 10 ml/minute)
- NSAIDs (Caution is advised when you are also taking non-steroidal anti-inflammatory drugs for pain relief such as ibuprofen or diclofenac. If administered together with Disodium Clodronate they may cause kidney problems)
- Certain antibiotics if used at the same time as Disodium Clodronate can cause low levels of clodron in the blood, therefore Disodium Clodronate should be administered with caution. If you are taking antibiotics together with Disodium Clodronate your doctor will perform tests to check your calcium blood level because it may fall below its normal blood level.

There is no evidence from clinical experience that sodium clodronate interacts with other medication such as steroids, diuretics, analgesics or chemotherapeutic agents.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy

Make sure you tell your doctor immediately if you are pregnant or likely to become pregnant as you should not receive Disodium Clodronate during pregnancy.

Breast-feeding

You should not breast feed while you are being treated with Disodium Clodronate. Breast-feeding should be discontinued before commencing treatment with Disodium Clodronate. Do not restart breast feeding until your doctor tells you it is safe to do so.

Driving and using machines

There is no reason why you cannot continue driving between courses of Disodium Clodronate.

Important information about some of the ingredients of Disodium Clodronate

Disodium Clodronate contains 8.32 mmol (or 191.25 mg) of sodium per dose. This needs to be taken into consideration by patients on a controlled sodium diet.
UKPAR Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion
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• you are a child (Disodium Cladronate should not be used in children),
• you are pregnant, likely to become pregnant or if you are breast feeding,
• you are taking other bisphosphonates,
• you are also taking non-steroidal anti-inflammatory painkillers (NSAIDS), e.g. ibuprofen or diclofenac,
• you are taking antibiotics,
• you have or have had pain, swelling or numbness of the jaw or a "heavy jaw feeling" or loosening of a tooth.

Take special care with Disodium Clodronate if:
• you have chronic kidney problems (concentrate should be administered with care to patients with chronic kidney problems; it is recommended that appropriate monitoring of kidney function be carried out during treatment).
• you are having dental treatment or have to undergo dental surgery, tell your dentist that you are being treated with a bisphosphonate, such as Disodium Clodronate - a dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with other risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).
Closeness of jaw (pain, swelling and infection) of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis which is an inflammation of the bone) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates.

Before taking Disodium Clodronate, you must tell your doctor if you have, or have ever had, any of the following disorders.
• any chronic kidney problems,
• any dental problems.
Your doctor may have to adjust your dose.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
The following medicines can affect or be affected by treatment with Disodium Clodronate:

3. HOW TO USE DISODIUM CLODRONATE

Always use Disodium Clodronate exactly as your doctor has told you. You should check with your doctor if you are not sure.
You need to take plenty of fluids (such as water) before, during and after your treatment.
Disodium Clodronate can be given as a single infusion or as multiple infusions as follows:
Single infusion: 1500 mg of Disodium Clodronate is diluted in either 500 ml of 0.9% w/v saline or 5% glucose solution and is given intravenously over a period of 4 hours.
Multiple infusions: 300 mg of Disodium Clodronate is diluted in either 500 ml of 0.9% w/v saline or 5% glucose solution and is given intravenously over a 2 hour period on successive days. If necessary your doctor may continue this daily treatment for up to a maximum of 7 days. The dosage may be reduced if your kidneys are not working properly. Your doctor will perform regular tests to monitor your medical condition during your treatment.

Response: Whichever method of infusion is used, most patients will achieve normal calcium levels in the blood within 5 days. For those who do not achieve a clinically acceptable serum calcium level, the infusion with Disodium Clodronate may be repeated.

Further Treatment: The length of time that a clinically acceptable serum calcium level is maintained after infusion of Disodium Clodronate varies considerably from patient to patient. Renal (kidney) function and serum calcium levels should be monitored during therapy. Dose reduction is recommended if deterioration in renal (kidney) function becomes apparent (see below). Treatment should be stopped if hypocalcaemia (low levels of calcium in the blood) develops, and serum calcium levels should be monitored to determine whether further treatment is required.

Renal Impairment:
There are no studies at present on which to base recommendations for dose reduction in patients with renal
(kidney) impairment when considering the option of a single 1500 mg infusion in hypercalcaemia which is a condition where there is an abnormally high level of calcium in the blood.

The dose of clodronate should be reduced in renal (kidney) impairment according to how efficiently the kidney is removing creatinine and other waste material from the blood when using divided intravenous doses of 300 mg. Therefore, in mild renal (kidney) impairment with creatinine clearance of 50 - 80 ml/minute a 25% reduction in dose is recommended, in moderate renal (kidney) impairment (10 - 50 ml/minute) a 50% reduction in dose is recommended. Sodium clodronate should not be used in patients with creatinine clearance below 10 ml/minute.

**Children:**
Disodium Clodronate should not be used in children.

**Elderly:**
There are no special dosage recommendations in the elderly. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

If you receive more Disodium Clodronate than you should Because the treatment with Disodium Clodronate is strictly monitored, it is unlikely that you will receive more Disodium Clodronate than you should. No reports of overdose with clodronate have been received. However, if you administer more Disodium Clodronate than you should, symptoms of overdose may include:
- fatal renal failure
- transient increases in serum creatinine, a waste product in the blood suggesting that overdosage of intravenous clodronate may lead to reduced renal function.
- hypocalcaemia, which is a deficiency of calcium in the blood may develop up to 2 or 3 days following the overdose. If you think that you have received too much Disodium Clodronate, speak to your doctor immediately.

If any of these changes do occur, they are unlikely to cause any noticeable symptoms. If any of these changes do occur, they are unlikely to cause any noticeable symptoms. Immediately after Disodium Clodronate your doctor will test for the presence of protein in your urine.

Periodically tests will be carried out during treatment to ensure that your kidneys are working properly and to monitor the level of calcium in your blood. Rarely, this type of drug has caused difficulty in breathing.

If you experience any of these side effects or any other side effects not mentioned above, consult your doctor.

5. **HOW TO STORE DISODIUM CLODRONATE**

This medicine will be stored in the pharmacy and made up in a special area before the doctor or nurse gives it to you. It should be kept in the original package, out of the reach and sight of children.

Do not take Disodium Clodronate after the expiry date which is stated on the blister and/or bottle and the box after "EXP". The expiry date refers to the last day of that month. An expiry date is given on the outer carton and vial of the product. It should not be used after this date.

**Solution in the original vial**
Concentrate should be stored below 25°C.

**Diluted solution**
The product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER INFORMATION**

What Disodium Clodronate contains:
If a Disodium Clodronate dose is skipped
Because Disodium Clodronate is administered by medical personnel, it is unlikely that you will miss a dose. However, if medical personnel have forgotten to administer more than one dose, you should contact your doctor.
Treatment duration is decided by your doctor. He/She will decide how long you should receive treatment. You should continue with the treatment as long as your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Disodium Clodronate can cause side effects, although not everybody gets them. Your doctor will discuss these with you.

The following frequencies are used in the evaluation of side effects:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>more than 1 in 10 patients treated</td>
</tr>
<tr>
<td>Common</td>
<td>less than 1 in 10, but more than 1 in 100 patients treated</td>
</tr>
<tr>
<td>Uncommon</td>
<td>less than 1 in 100, but more than 1 in 1,000 patients treated</td>
</tr>
<tr>
<td>Rare</td>
<td>less than 1 in 1,000, but more than 1 in 10,000 patients treated</td>
</tr>
<tr>
<td>Very rare</td>
<td>less than 1 in 10,000 patients treated, not known (cannot be estimated from the available data)</td>
</tr>
</tbody>
</table>

Skin reactions, such as rash, redness or itching may occur. These effects are usually mild. However, if they persist or become troublesome consult your doctor.
Rarely, this type of drug has caused difficulty in breathing. Bronchospasm has been experienced rarely in patients with and without a previous history of asthma.
Unwanted effects on the kidneys have been reported. This appears to be more common in patients receiving non-steroidal anti-inflammatory drugs (NSAID'S used for pain relief such as ibuprofen or diclofenac, although no definite association has been established.
Isolated cases of osteonecrosis of the jaw (dead tissue in the jaw bone) have been reported, mainly in patients who have been treated in the past with bisphosphonates such as zoledronate and pamidronate. Symptoms include pain, swelling or numbness of the jaw, a “heavy jaw feeling” or loosening of a tooth.
Occasionally increased levels of serum parathyroid hormone, certain enzymes and creatinine (a waste product) have been reported. Rarely, calcium blood levels have fallen below

The active substance is clodronic acid disodium (as the tetrahydrate).
The other ingredients are sodium hydroxide and water for injections.

What Disodium Clodronate looks like and contents of the pack:
Disodium Clodronate is available in 5 ml colourless vials, packed into cartons containing 1 vial. The polypropylene disk in the metal cap is yellow.

Marketing Authorisation Holder
SINDAN Ltd.
81/8 Shepherds Hill
London N6 5RG
United Kingdom
Tel: +44(0)208 348 7759

Manufacturer
S.C. SINDAN-PHARMA S.R.L.
11 Ion Mihalache Blvd., District 1
011171 Bucharest, Romania
Tel: (+40) 21 318 17 67; (+40) 21 318 17 67
Fax: (+40) 21 312 44 99
E-mail: inforo@actavis.com

DATE OF LAST REVISION: December 2007
UKPAR Disodium clodronate 60 mg/ml Concentrate for Solution for Infusion

LABELLING

Carton

Disodium Clodronate 60 mg/ml
Concentrate for solution for infusion

Disodium Clodronate (as tetrahydrate) 300 mg/5 ml

Composition: Each 5 ml vial contains 300 mg disodium clodronate (as tetrahydrate), sodium hydroxide, water for injections

Store in the original package

Use as directed by a physician

Please read the enclosed package leaflet

Keep out of the reach and sight of children

SINDAN

PB 20 00342

Label

Disodium Clodronate 60 mg/ml
Concentrate for solution for infusion

Disodium Clodronate (as tetrahydrate) 300 mg/5 ml

Composition: Each 5 ml vial contains 300 mg disodium clodronate (as tetrahydrate), sodium hydroxide, water for injections

Must be diluted before use

For intravenous use only

Marketing Authorisation Holder:
SINDAN Ltd.
51/8 Shephords Hill
London N6 5RG
United Kingdom

PL 22191/0001

Batch: Expiry:

PS 20 02220