Aminobiphosphonates in Osteoporosis: A Review

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Abstract: Osteoporosis is a disease of great social impact, in recent years has assumed increasing importance, due to the progressive ageing of the population and the consequent increase of its complications, first of all femoral and vertebral fractures. Various treatment strategies has been employed to overcome, Aminobiphosphonate is one of them & they represents a major advance in the treatment of musculoskeletal disorders and they are now amongst the most commonly used agents in clinical practice. Bisphosphonates are analogues of inorganic pyrophosphate and are inhibitors of bone resorption. Many derivatives have been developed for the treatment of enhanced bone resorption. In this review, we explore the potential applications of that concept by summarizing the bone diseases and candidate proteins that will benefit from the proposed bone delivery approach. A selective synopsis of BP synthesis is presented to highlight the synthesis of functional BPs suitable for covalent attachment to proteins.

Keywords: Aminobiphosphonate, Osteoporosis, Pyrophosphates, Osteoclast, Osteoblast.

Introduction

Bisphosphonates are pyrophosphate analogues in which the oxygen bridge has been replaced by a carbon with various side chains P-C-P. These compounds have been known to the chemist since the 19th century, the first synthesis dating back to 1865. After discovering that they can effectively control calcium phosphate formation and dissolution in-vitro, as well as mineralization and bone resorption in-vivo. They were developed and used in the treatment of bone diseases.

Osteoporosis:

Osteoporosis is described by the World Health Organization as a ‘progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture’. More than one-third of adult women and one in five men will sustain one or more osteoporotic fractures in their lifetime. Common sites of fracture include the vertebral bodies, distal radius, proximal femur and the proximal humerus.1

Etiology:

The most common cause of osteoporosis arises from estrogen deficiency that begins some years before the time of menopause. The skeleton comprises approximately 20% trabecular bone and 80% cortical bone and undergoes a continual process of resorption and formation, governed by the activity of bone cells in bone remodelling units. Estrogen deficiency accelerates the normal of bone tissue, but the net activity of bone resorbing cells (osteoclasts) is greater than that of bone forming cells (osteoblasts). This gives rise to thinning of the cortices of bones, thinning of trabecular bone and loss of trabecular elements.1 (Figure-1)
Figure-1: Comparison of structure of trabecular bone in health (left panel) and osteoporosis (right), illustrating the architectural damage including trabecular thinning and perforation.

**Diagnosis of Osteoporosis:**
The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). BMD at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 standard deviations (SD) or more below the young female adult mean (T-score less than or equal to −2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures.1

**Classifications of Osteoporosis:**

**The Four types of Osteoporosis**

**Primary osteoporosis**
Primary osteoporosis is the most common type of osteoporosis. It is more common in women than men. A person reaches peak bone mass (density) at about age 30; after that, the rate of bone loss slowly increases, while the rate of bone building decreases.

In women, accelerated bone loss usually begins after monthly menstrual periods stop, when a woman’s production of estrogen slows down (usually between the ages of 45 and 55). In men, gradual bone thinning typically starts at about 45 to 50 years of age, when a man’s production of testosterone slows down.

**Secondary osteoporosis**
Secondary osteoporosis has the same symptoms as primary osteoporosis. But it occurs as a result of having certain medical conditions, such as hyperparathyroidism, hyperthyroidism, or leukemia. It may also occur as a result of taking medicines known to cause bone breakdown, such as oral or high-dose inhaled corticosteroids (if used for more than 6 months), too high a dose of thyroid replacement, or aromatase inhibitors (used to treat breast cancer). Secondary osteoporosis can occur at any age.

**Osteogenesis imperfecta**
Osteogenesis imperfecta is a rare form of osteoporosis that is present at birth. Osteogenesis imperfecta causes bones to break for no apparent reason.

**Idiopathic juvenile osteoporosis**
Idiopathic juvenile osteoporosis is rare. It occurs in children between the ages of 8 and 14 or during times of rapid growth. There is no known cause for this type of osteoporosis, in which there is too little bone formation or excessive bone loss. This condition increases the risk of fractures.2

**Treatment of Osteoporosis:**3

- Treatment for osteoporosis may involve:
  - a. Lifestyle changes, such as diet and exercise
  - b. Taking calcium and vitamin D
  - c. Using medications
- Medicines used to treat osteoporosis include:
  - a. Bisphosphonates (the main drugs used to prevent and treat osteoporosis in postmenopausal women)
  - b. Estrogens, teriparatide, raloxifene and calcitonin
There are two surgeries used to treat severe, disabling pain from spinal fractures due to osteoporosis:

a. Kyphoplasty
b. Vertebroplasty

Exercise plays a key role in preserving bone density in older adults. Some of the exercises recommended to reduce your chance of a fracture include:

a. Weight-bearing exercises -- walking, jogging, playing tennis, dancing
b. Free weights, weight machines, stretch bands
c. Balance exercises -- tai chi, yoga
d. Rowing machines

Aminobiphosphonates:

**Introduction:**
Bisphosphonates are analogues of inorganic pyrophosphate and are inhibitors of bone resorption. Bisphosphonates are pyrophosphate analogues in which the oxygen bridge has been replaced by a carbon with various side chains P-C-P. Bisphosphonates (BPs), which exhibit a strong affinity to bone mineral under physiological conditions. Systemic administration of BPs commonly results in 20–50% deposition of the molecules at bone tissues, with minimal accumulation at other sites. Bisphosphonates are known to inhibit biochemical markers of bone formation in-vivo, but it is unclear to what extent this is a consequence of osteoclast inhibition or a direct inhibitory effect on cells of the osteoblast lineage. BPs are structurally analogous to the endogenous inorganic phosphate, pyrophosphoric acid. Replacement of the central oxygen (O) atom in the pyrophosphate with a carbon (C) in BPs allows one to incorporate additional functionalities to the BPs. Bisphosphonates have been developed primarily as potent inhibitors of osteoclast-mediated bone resorption. This bioactivity largely results from their P–C–P bond and C-bound lateral chain R. Both P–C–P structure and C–OH substituent are responsible for bisphosphonate binding to the mineralized bone matrix, whereas the R-substituting group determines their capability of inhibiting osteoplastic bone resorption.4 5

The structure of pyrophosphoric acid and a geminal BP. Common members of the BP family

<table>
<thead>
<tr>
<th>Aminobiphosphonate</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
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<tbody>
<tr>
<td><strong>Non-Nitrogen Containing</strong></td>
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</tr>
<tr>
<td>Etidronate</td>
<td>-OH</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Clodronate</td>
<td>-Cl</td>
<td>-Cl</td>
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<tr>
<td><strong>Nitrogen Containing</strong></td>
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<tr>
<td>Pamidronate</td>
<td>-OH</td>
<td>(-CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Alendronate</td>
<td>-OH</td>
<td>(-CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;-NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Nericronate</td>
<td>-OH</td>
<td>(-CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;5&lt;/sub&gt;-NH&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Incadronate</td>
<td>-H</td>
<td>[R]</td>
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<tr>
<td>Olpadronate</td>
<td>-OH</td>
<td>(-CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;-N-NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<tr>
<td>Riserdronate</td>
<td>-OH</td>
<td>-H&lt;sup&gt;+&lt;/sup&gt;</td>
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<tr>
<td>Zelodronate</td>
<td>-OH</td>
<td>[N]</td>
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**Table 1: Aminobiphosphonates**

Depending on the structural details of a BP it is possible to increase the bone affinity of BPs (e.g., – OH on the central C), to impart a variety of pharmacological activities to BPs and to enhance...
the potency of the main pharmacological activity of BPs, namely the inhibition of osteoclast-mediated bone resorption.

Structure-Activity Relationships (SAR):

- Bisphosphonate moiety is essential for hydroxyapatite affinity. The monophosphonates are not active!
- Side chain (R₁ and R₂ groups): responsible for inhibition of resorption. A single carbon atom between phosphate residues required
- Dichloro (clodronate) and hydroxy-alkyl (etidronate) derivatives (first generation agents): Inhibit bone mineralization (at higher doses) and resorption (see mechanism below)
- Incorporation of an OH at C1 optimizes affinity for hydroxyapatite and increases anti-resorptive activity (increases both components of activity).
- Incorporation of a 4-chlorothiophenyl substituent at C1 (tiludronate): 10X more active than etidronate
- Incorporation of an aminoalkyl side chain at C1 increases anti-resorptive potency 10-fold, allows for separation between antiresorptive and bone mineralization effects (see mechanism below).
- Length of carbon chain important: 2-5 is tolerated and 3 Cs is optimal as in alendronate. Alendronate is about 1000X more potent than etidronate and pamidronate is 100X more active than etidronate.
- Incorporation of a nitrogen heterocycle (pyridine) at C1 further enhances anti-resorptive potency (Third generation agents: Risedronate): Risedronate is as much as 5000X more potent than etidronate.

Mechanism of Action:

The Mechanism of aminobiphosphonates can explain from its action on osteoporotic bone via its action on osteoclast & bone resorption process. It involve following steps: 

Uptake of aminobiphophonates by osteoclast:
- The mechanism behind the uptake of aminobiphosphonates from surface of the bone into the osteoclast cytoplasm is found to be different for different aminobiphosphonates.
- Uptake of the Non-nitrogen containing aminobiphosphonates occur through active reabsorption process in which acid secreted onto the bone surface could release the bound state aminobiphosphonates which can be uptake through the ruffled border adjacent to the resorption lacunae.
- Incadronate doesn’t require active bone reabsorption as it affect osteoclast bone attachment and this was studied in in-vivo study in the oc/oc mouse.
- Earlier studies which involve the administration of pharmacological relevant dose of highly potent aminobiphosphonates like alendronate having uptake mechanism for
through the plasma membrane. Osteoclasts gather through the ruffled border the content of the resorption lacunae and by the process of transcytosis translocate it through the cell. Physically located internalized vesicles within the cytoplasm, derived from the membrane of the ruffled border, by the vesicular border remain separated from the cytoplasmic content. Passive diffusion could be one process for crossing these membrane, although active or facilitated transport may involve as suggested by recent evidences.

Recently, by combining alendronate with increasing dose of clodronate, the suppressed effects of alendronate were found on its target intracellular pathway within the osteoclast, which have its independent mechanism to work. This suggest a participation of a structure specific process, which showed that there was a competition for entry mechanism into the cytoplasm.

Molecular Target of the Nitrogen-containing Bisphosphonates: Farnesyl Diphosphate Synthase

FPP synthase identify as the relevant molecular target by the Number of studies that suggest that this enzyme have upstream in the pathway controlling both synthesis of cholesterol and isoprenylation, so it become the critical target of the N-BPs in the osteoclast. Recently, from the in-vivo studies of the several N-BPs, including alendronate, risedronate and ibandronate, but not for the simple bisphosphonates, clodronate and etidronate this molecular action has been confirmed.

In the cholesterol biosynthetic pathway (Figure-2) farnesyl diphosphate (FPP) synthase is an enzyme that is responsible for producing the isoprenoid lipids FPP (15 carbon) and geranylgeranyl diphosphate (GGPP; 20 carbon). FPP isoprenoid could be involved to form squalene and ultimately cholesterol, but the critical step for the N-BPs suppression of osteoclastic bone resorption is its conversion to GGPP.

Isoprenylation is the process which involves the transfer of a lipid group of farnesyl (farnesylation) or geranyl-geranyl (geranylgeranylation) onto an amino acid residue (cysteine) in characteristic carboxy-terminal motifs (eg, Cys-Ala-Ala-X). Suppression of FPP synthase by the N-BPs results into decline in the levels of both FPP and subsequently of GGPP. The consequent loss of protein geranyl-geranylation followed by osteoclast inactivation. This effect has been demonstrated by alendronate, ibandronate or risedronate in the inhibitory concentration of above aminobiphosphonate.

Furthermore, HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors, lovastatin and mevastatin also mimicked the action of N-BP (upstream of FPP synthase), which can be also blocked by the addition of geranylgeraniol.

The signalling pathways are remains to be determined which are involve geranylgeranylated small GTPases which are affected by bisphosphonates and finally lead to osteoclast apoptosis. Most proximal to the GTPases is, the one mTOR (mammalian target of rapamycin) or another one is S6K (ribosomal protein S6 kinase) signalling pathway. When geranyl-geranylation is blocked in the osteoclast, signalling through this path is suppressed. Downstream significance of N-BP or rapamycin therapy include activation of caspases, pro-apoptotic kinase, and MST1 (mammalian sterile-zero-like kinase). MST1 was activated during apoptosis caused by NBPs, lovastatin, and clodronate, which was identified as a pro-apoptotic signalling intermediate.
downstream of the bisphosphonates. MST1 kinase acts as a substrate for caspases 3, 7 and 9 and as an activator of these caspases (Figure 3).

The ruffled border acts a hallmark of active osteoclasts, which is a convoluted membrane that faces the bone surface. Disappearance of the ruffled border provides morphologic evidence for mechanism-based osteoclast inactivation and could explain the lack of acid extrusion caused by alendronate in isolated osteoclasts. Ruffled border formation is a process that is highly dependent on cytoskeletal function and strongly regulated by geranylerganylated GTPases, such as Rac and Rho.

![Figure 2: Schematic of the cholesterol biosynthetic pathway. Sites of inhibition for the nitrogen-containing bisphosphonates (N-BPs; farnesyl diposphate (FPP) synthase) and statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase) are indicated. The basic structures of FPP and geranyl-geranyldiphosphate (GGPP) are also shown. DMAPP—dimethyl allyl diphosphate; GTPase—guanosine triphosphate; IPP—isopentenyl diphosphate.](image)

![Figure 3: Schematic for nitrogen-containing bisphosphonate (N-BP) and clodronate molecular actions in suppressing osteoplastic bone resorption. GTPase—guanosine triphosphates; IPP—isopentenyldiphosphate; DMAPP—dimethylallyl diphosphate.](image)

**Classification of Aminobiphosphonates**:  
1) 1st Generation  
A) ETIDRONATE  

![Molecular Weight: \( \text{C}_3\text{H}_5\text{O}_7\text{P}_2 \), Molecular Weight: 206.028244 Da](image)

The drug had been approved by FDA on 1 September 1977 for **PROCTOR AND GAMBLE** under the brand name **DIDRONEL**.  
**Brand Names**: Cintichem, Technetium 99m, Hedspa, Dequest 2010, Didronel, Ferrofos 510, Osteoscan.  
**Physico-chemical Properties**:  
**Appearance**: light beige powder  
**Stability**: Stable. Incompatible with strong oxidizing agents.
**Specific Gravity:** 1.45
**Melting Point:** 199°C
**Log P:** -3.8
**Water solubility:** 1.15e+01g/l

**Pharmacokinetic Summary:**
- **Oral Bioavailability:** 1.6%
- **Volume of distribution:** 1.4 L/kg
- **Terminal t1/2:** >90 days
- **Plasma Clearance:** 6 hrs.

**Targets & Action:**
1. Hydroxyapatite - Antagonist
2. Receptor-type tyrosine-protein phosphatase S - Inhibitor
3. V-type proton ATPase catalytic subunit A - Inhibitor

**Indications:**
- Paget’s disease
- Heterotopic Ossification

**Adverse Reactions:** Gastrointestinal Complaints (Diarrhoea, Nausea), Increased or Recurrent Bone Pain at Pagetic Sites

**Drug Interaction:** Warfarin, Aluminium, Sucralfate.

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**B) CLODRONATE**

[Dichloro (phosphono) methyl] phosphonic acid

**Molecular Formula:** CH₄Cl₂O₆P₂, **Molecular Weight:** 244.892384 Da

The Drug has not been approved by FDA still. The application had been filled by BERLEX LABORATORIES under the name BONEFOS, FDA declared further trial awaited report for this drug on 11 May 2005.

**Brand Names:** Acidum Clodronicum [INN-Latin], Bonefos, Clasteon, Loron, Ostac

**Physico-Chemical Properties:**
- **State:** Solid
- **Melting Point:** 250°C
- **Water Solubility:** 395mg/ml
- **Log P:** -2.4
- **Density:** 2.306 g/cm³

**Pharmacokinetic Summary:**
- **Absorption:** Around 1-3% from GIT
- **Volume of distribution:** 20 L
- **Protein Binding:** 2%-36%
- **Terminal t1/2:** 13 hours

**Targets & Action:**
1) ADP/ATP translocase 1: Inhibitor
2) ADP/ATP translocase2: Inhibitor
3) ADP/ATP translocase3: Inhibitor
4) Hydroxyapatite: Antagonist

**Indications:**
- Malignancy-related hypercalcemia
- Osteolytic bone metastases

**Adverse Reactions:** Hypersensitivity, Rashes, Hypocalcaemia, Increased Parathyroid, Hormone Level

**Drug Interaction:** Antacid (calcium, iron, magnesium or aluminium-containing preparations), Aminoglycosides, Estramustine and Calcium lowering agents.

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**C) TILUDRONATE**

[(4-chlorophenyl) sulfanyl-phosphonomethyl] phosphonic acid

**Molecular Formula:** C₇H₇ClO₆P₂S, **Molecular Weight:** 318.608284 Da

The drug had been approved by FDA on 7 March 1997 for SANOFI AVENTIS US under the brand name SKELID.

**Brand name:** Skelid.
Physico-Chemical Properties:

State: Solid
Log P: -0.6
Water solubility: 6.97e+00 g/l
Density: 1.827 g/cm³

Pharmacokinetic Summary:

Oral bioavailability: 6%
Protein binding: Approx. 90%
T₁/₂: 150 hours

Targets & Action:
1. Hydroxyapatite: Antagonist
2. V-type proton ATPase catalytic subunit A: Inhibitor
3. Tyrosine-protein phosphatase non-receptor type 1: Inhibitor

Indications:
Paget’s disease

Adverse Reactions:
Painful or difficult swallowing, Severe Heartburn, Diarrhea, Joint Pain, Rashes.

Drug Interactions: Indomethacin, Warfarin, Diclofenac, Calcium.

2) 2nd Generation:

A) PAMIDRONATE ¹⁰, ²⁴-²⁷

Molecular Formula: C₃H₁₁NO₇P₂, Molecular Weight: 235.069504 Da

The drug had been approved by FDA on 31 October 1991 for NOVARTIS under the brand name AREDIA.

Brand names: Aredia, Amidronate, Aminomux

Physico-Chemical Properties:

State: Solid powder
Color: White to practically white

Log P: -4.7
Solubility: In water and in 2N sodium hydroxide, sparingly soluble in 0.1N hydrochloric acid and in 0.1N acetic acid
Water solubility: 1.58e+01 g/l
Density: 1.999 g/cm³

Pharmacokinetic Summary:

Absorption: Rapid after IV administration
Protein binding: Approx. 54% to human serum protein
Metabolism & Excretion: Not metabolized but eliminated though renal excretion
T₁/₂: mean ± SD elimination half-life is 28 ± 7 hours
Renal Clearance: 49 ± 28 mL/min

Targets & Action:
1. Farnesyl pyrophosphate synthetase: Inhibitor
2. Hydroxyapatite: Antagonist

Indications:
Hypercalcemia of Malignancy
Paget’s disease
Osteolytic Bone Metastases of Breast Cancer
Osteolytic Lesions of Multiple Myeloma

Adverse reactions: Fluid overload, Hypertension, Abdominal pain, Bone pain, Urinary Tract Infection.

Drug Interactions: Loop diuretic, potentially nephrotoxic drug, Thalidomide

B) ALEDRONATE ¹⁰, ²⁸-³¹

Molecular Formula: C₄H₁₃NO₇P₂, Molecular Weight: 249.096044 Da

The drug had been approved by FDA on 31 October 1991 for NOVARTIS under the brand name AREDIA.

Brand names: Aredia, Amidronate, Aminomux

Physico-Chemical Properties:

State: Solid powder
Color: White to practically white
The drug had been approved by FDA on 29 September 1995 for **MERCK AND CO INC.** under the brand name **FOSAMAX**.

Brand names: Adronat, Alendros, Arendal, Fosamax, Fosamax Plus D, Onclast.

**Physico-Chemical Properties:**

**State:** Solid

**Color & Nature:** White, Crystalline & non-hygroscopic powder

**Solubility:** soluble in water, very slightly soluble in alcohol, and practically insoluble in chloroform.

**Melting Point:** 234°C

**Water solubility:** 1mg/m

**Log P:** -4.3

**pKa:** 2.72(at 25°C)

**Density:** 1.857 gm/cm³

**Pharmacokinetic summary:**

**Mean oral bioavailability:** 0.64% for doses 5 to 70 mg in women

**Volume of distribution:** 28 L

**Protein Binding:** Approx. 78%

**Metabolism:** Not metabolized

**Clearance:** Renal (71 mL/min), Systemic (<200 mL/min)

**Target & Actions:**

1. **Farnesyl pyrophosphate synthetase:** Inhibitor

2. **Hydroxyapatite:** Antagonist

3. **Tyrosine-protein phosphatase non-receptor type 4:** Inhibitor

4. **Receptor-type tyrosine-protein phosphatase S:** Inhibitor

5. **Receptor-type tyrosine-protein phosphatase epsilon:** Inhibitor

6. **V-type proton ATPase catalytic subunit A:** Inhibitor

**Indications:**

- Osteoporosis in postmenopausal women & men
- Glucocorticoid-induced osteoporosis
- Paget’s disease.

**Adverse Reactions:** Gastrointestinal Complaints (Diarrhea, Nausea), Abdominal pain, Musculoskeletal pain, Headache, Taste prevention.

**Drug Interaction:** Calcium supplements, Antacids, Other multivalent Cations, Hormone Replacement Therapy

C) **IBANDRONATE**

{1-Hydroxy-3-[methyl (pentyl) amino]-1, 1-propanediyl} bis (phosphonic acid)

**Molecular Formula:** C₉H₂₃NO₇P₂, **Molecular Weight:** 319.229004 Da

The drug had been approved by FDA on 16 May 2003 for **HOFFMANN LA ROCHE** under the brand name **BONIVA**.

**Brand names:** Bondronate, Boniva, Bonviva

**Physico-Chemical Properties:**

**State:** Solid

**Color & nature:** White to off white powder

**Solubility:** Freely soluble in water, practically insoluble in organic solvents.

**Log P:** -2.1

**Density:** 1.45 g/cm³

**Water solubility:** 1.34e+01 g/l

**Pharmacokinetic Summary:**

**Oral bioavailability:** 0.6%

**Plasma t₁/₂:** 10-60 hr.

**Protein binding:** Approx. 86%

**Volume of distribution:** >90 L

**Target & Actions:**

1. **Farnesyl pyrophosphate synthetase:** Inhibitor

2. **Hydroxyapatite:** Antagonist
Indications:
- Treatment of Postmenopausal Osteoporosis
- Treatment of osteoporosis is based on clinical data of one year duration.

Adverse Reactions: Hypocalcaemia, Anaphylactic reactions, Renal impairment, Musculoskeletal Pain, Osteonecrosis of the Jaw

Drug Interaction: Melphalan/Prednisolone, Bone Imaging Agents, Tamoxifen

B) RISEDRONATE

![Chemical Structure of Risedronate](image)

(1-hydroxy-1-phosphono-2-pyridin-3-yethyl) phosphonic acid

Molecular Formula: C_{9}H_{11}NO_{3}P_{2}, Molecular Weight: 283.112264

The drug had been approved by FDA on 27 March 1998 for WARNER CHILCOTT LLC under the brand name ACTONEL.

Brand names: Actonel, Benet

Physico-Chemical Properties:
- State: Solid
- Color & nature: White to off white crystalline powder
- Solubility: soluble in pH 7.0 potassium phosphate dibasic solution, 0.1 N sodium hydroxide, and water; very slightly soluble in 0.1 N hydrochloric acid, practically insoluble in ethanol, and insoluble in isopropanol.
- Log P: -3.6
- Density: 1.871 g/cm³
- Water Solubility: 1.04e+01 g/l
- Pharmacokinetic Summary:
  - Absorption: ~1 hr after oral dose
  - Volume of distribution: 13.8 L/kg
  - Protein Binding: ~24%
  - t½: 1.5 hr.

Clearance: 122 mL/min

Target & Actions:
1. Farnesyl pyrophosphate synthetase: Inhibitor
2. Hydroxyapatite: Antagonist

Indication:
- Treatment & prevention of osteoporosis in postmenopausal women
- Treatment of osteoporosis in men
- Treatment & prevention of glucocorticoid-induced osteoporosis in men & women
- Paget’s disease

Adverse Reaction: Abdominal pain, Headache, Dyspepsia, Nausea, Rash, Pertussis, Osteonecrosis of jaw, musculoskeletal pain

Drug Interaction: Antacids and calcium supplements which contain polyvalent cations, Hormone replacement therapy (HRT), H₂-blockers and PPIs.

3) 3rd Generation:
ZOLEDRONATE

![Chemical Structure of Zoledronate](image)

[1-Hydroxy-2-(1H-imidazol-1-yl)-1,1-ethanediyl]bis(phosphonic acid)

Molecular Formula: C_{9}H_{10}N_{2}O_{7}P_{2}, Molecular Weight: 272.089624

The drug had been approved by FDA on 16 April 2007 for NOVARTIS under the brand name RECLAST.

Physico-Chemical properties:
- State: Solid
- Color & nature: White crystalline powder
- Log P: -4.2
- Density: 2.136 g/cm³
Water solubility: 3.27e+00 g/l
Pharmacokinetic summary:
Absorption: Approx. 1% oral absorption
Protein Binding: ~22%
$\text{t}_{1/2}$: 146 hrs.
Clearance: 3.7 +/- 2.0 L/h

Target & actions:
1. Farnesyl pyrophosphate synthetase: Inhibitor
2. Hydroxyapatite: Antagonist
3. Geranyl-geranyl pyrophosphate synthetase: Inhibitor

Indications:
- Hypercalcemia of Malignancy
- Multiple Myeloma and Bone Metastases of Solid Tumors

Adverse reactions: Fever, constipation, nausea, dyspepsia, Bone pain

Drug interaction: Aminoglycoside, loop diuretic, thalidomide.

Conclusion:
The review indicate about the different strategies has been available for the treatment of osteoporosis along with its reasons & etiology. The review had been mainly focused on the one of the potential treatment that is available for the treatment to osteoporosis & other bone related diseases. The aminobiphosphonate is a very good option than the other therapies available for the bone disorders such as physiotherapy, surgeries, acupuncture, Homeopathy & etc. Aminobiphosphonate are the drug of choice which is readily available with well tolerance to patients& not having life-threatening side effects. So the review article includes all the general information regarding the each generation of aminobiphosphonate with its indication. So form the review it can be concluded that there is a need of investigation in this area as the osteoporosis is world-wide distributed disease by making the aminobiphosphonate as the marker for further investigation.

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