Interleukin-1 Receptor Antagonists

Antagonista del Receptor de la Interleucina 1; IL-1ra; IL-1i; Interleukin-1 Inhibitors.

Profile

Endogenous antagonists to interleukin-1 receptor block the actions of interleukin-1 (p.2325) and recombinant forms have been investigated in inflammatory and immune-modulated disorders.

Anakinra (p.19) is a human recombinant interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis.

Interleukin-2 Fusion Toxins

Toxinas de fusión de interleucina 2.

Profile

Interleukin-2 fusion toxin is produced by replacing the receptor binding domain of diphtheria toxin with sequences from interleukin-2, thus producing specific cytotoxicity in cells expressing the interleukin-2 receptor. The interleukin-2 fusion toxin denileukin diftitox (p.710) is used in the treatment of cutaneous T-cell lymphoma. The related compound DAB_{486} interleukin-2 has also been investigated in a variety of disorders.

Interleukin-6

B-cell Stimulatory Factor-2; BSF-2; Hepatocyte-Stimulating Factor; Hybridoma Growth Factor; IFN-β_2; IL-6; Interferon-β2.

Интерлейкин-6

Profile

Interleukin-6 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by many cell types and induces differentiation of B-lymphocytes and activation of T-cells. It has proinflammatory and pyrogenic properties and is involved in the regulation of immune responses and inflammation. Interleukin-6 has also been implicated in haematopoiesis.

Atexakin alfa is human recombinant interleukin-6 under investigation.

Since overproduction of interleukin-6 plays a crucial role in the pathogenesis of chronic inflammatory diseases, interleukin-6 antibodies (p.2326) and interleukin-6 receptor antagonists (p.2326) are being investigated or used as therapeutic agents.

Interleukin-6 Antibodies

IL-6 Antibody.

Elsilimomab *(rINN)*

Elsilimomabum. Immunoglobulin G1, anti-(human interleukin 6) (mouse monoclonal B-E8 heavy chain), disulfide with mouse monoclonal B-E8 κ-chain, dimer.

Эльсилимомаб

CAS — 468715-71-1.

Profile

Monoclonal antibodies to interleukin-6 (p.2326) are under investigation for the treatment of disorders including post-transplant lymphoproliferative disorders and renal cell carcinoma.

Elsilimomab is an interleukin-6 monoclonal antibody under investigation.

Interleukin-6 Receptor Antagonists

Tocilizumab *(USAN, rINN)*

Atlizumab; MRA; R-1569; Tocilizumabum. Immunoglobulin G1, anti-(human interleukin 6 receptor) (human-mouse monoclonal MRA heavy chain), disulfide with human-mouse monoclonal MRA κ-chain, dimer.

Тоцилизумаб

CAS — 375823-41-9.

Profile

Antagonists to the interleukin-6 receptor block the actions of interleukin-6 (p.2326) and are under investigation for rheumatoid arthritis, systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease, Crohn's disease, and haemolytic anaemia.

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder. It is also used for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis.

◊ References.

1. Nishimoto N, *et al.* Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000; **95:** 56–61.
2. Ito H, *et al.* A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. *Gastroenterology* 2004; **126:** 989–96.
3. Nishimoto N. Clinical studies in patients with Castleman's disease, Crohn's disease, and rheumatoid arthritis in Japan. *Clin Rev Allergy Immunol* 2005; **28:** 221–30.
4. Yokota S, *et al.* Clinical study of tocilizumab in children with systemic-onset juvenile idiopathic arthritis. *Clin Rev Allergy Immunol* 2005; **28:** 231–8.
5. Lipsky PE. Interleukin-6 and rheumatic diseases. *Arthritis Res Ther* 2006; **8** (suppl 2): S4. Available at: http://arthritis-research.com/content/8/S2/S4 (accessed 11/02/08)
6. Maini RN, *et al.* Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; **54:** 2817–29.
7. Paul-Pletzer K. Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 2006; **42:** 559–76.
8. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. *Nat Clin Pract Rheumatol* 2006; **2:** 619–26. Correction. *ibid.*; 691.
9. Kanda J, *et al.* Reversible cardiomyopathy associated with multicentric Castleman disease: successful treatment with tocilizumab, an anti-interleukin 6 receptor antibody. *Int J Hematol* 2007; **85:** 207–11.
10. Matsuyama M, *et al.* Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease. *Intern Med* 2007; **46:** 771–4.
11. Smolen JS, *et al.* OPTION Investigators. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; **371:** 987–97.
12. Yokota S, *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; **371:** 998–1006.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Actemra.

Interleukin-10

CSIF; Cytokine synthesis inhibitory factor; IL-10.

Интерлейкин-10

CAS — 130068-27-8.

Ilodecakin *(USAN, rINN)*

Ilodecakina; Ilodécakine; Ilodecakinum; Interleukin-10 (human clone pH15C); rhIL-10; Sch-52000.

Илодекакин

CAS — 149824-15-7.

Profile

Interleukin-10 is one of a number of polypeptides known collectively as interleukins (p.2325). It regulates the differentiation and proliferation of several immune cells including T-cells and B-cells. It is postulated that it has immunostimulant as well as immunosuppressive properties; it also has anti-inflammatory actions. Interleukin-10 is under investigation for inflammatory bowel disease, malignant neoplasms, skin disorders including psoriasis and reduction of scarring, rheumatoid arthritis, hepatitis C, and organ transplantation.

Ilodecakin is a recombinant form of interleukin-10 under investigation.

◊ References.

1. Asadullah K, *et al.* Interleukin-10 therapy—review of a new approach. *Pharmacol Rev* 2003; **55:** 241–69.
2. Braat H, *et al.* Interleukin-10-based therapy for inflammatory bowel disease. *Expert Opin Biol Ther* 2003; **3:** 725–31.
3. Weiss E, *et al.* The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. *J Am Acad Dermatol* 2004; **50:** 657–75.
4. Asadullah K, *et al.* Interleukin-10: an important immunoregulatory cytokine with major impact on psoriasis. *Curr Drug Targets Inflamm Allergy* 2004; **3:** 185–92.
5. Vicari AP, Trinchieri G. Interleukin-10 in viral diseases and cancer: exiting the labyrinth? *Immunol Rev* 2004; **202:** 223–36.
6. Mocellin S, *et al.* Interleukin-10 and the immune response against cancer: a counterpoint. *J Leukoc Biol* 2005; **78:** 1043–51.
7. Mege JL, *et al.* The two faces of interleukin 10 in human infectious diseases. *Lancet Infect Dis* 2006; **6:** 557–69.

Interleukin-12

IL-12.

Интерлейкин-12

Edodekin Alfa *(USAN, rINN)*

Edodekina alfa; Édodékine Alfa; Edodekinum Alfa; Ro-24-7472/000.

Эдодекин Альфа

CAS — 187348-17-0.

Description. A recombinant human interleukin-12.

Profile

Interleukin-12 is one of a number of polypeptides known collectively as interleukins (p.2325). It is produced by macrophages and dendritic cells and enhances cellular immunity through induction of the activity of interferon-γ and cytotoxic T-lymphocytes. It has been investigated for the treatment of severe infections such as mycobacterial infections; it is worthy of note that children with a rare inherited susceptibility to fatal mycobacterial infections exhibit mutations in the interleukin-12 gene. Interleukin-12 is also under study for the treatment of various cancers, including as adenovirus-mediated gene therapy.

Edodekin alfa is human recombinant interleukin-12 under investigation for the treatment of renal cell carcinoma.

◊ References.

1. Mazzolini G, *et al.* Gene therapy of cancer with interleukin-12. *Curr Pharm Des* 2003; **9:** 1981–91.
2. Kikuchi T, *et al.* Vaccination of glioma patients with fusions of dendritic and glioma cells and recombinant human interleukin 12. *J Immunother* 2004; **27:** 452–9.
3. Trudeau C, *et al.* A single administration of recombinant human interleukin-12 is associated with increased expression levels of interferon-gamma and signal transducer and activator of transcription in healthy subjects. *J Clin Pharmacol* 2005; **45:** 649–58.
4. Sangro B, *et al.* Gene therapy of cancer based on interleukin 12. *Curr Gene Ther* 2005; **5:** 573–81.
5. Little RF, *et al.* Activity of subcutaneous interleukin-12 in AIDS-related Kaposi sarcoma. *Blood* 2006; **107:** 4650–7.

Intrinsic Factor

Antianemic Factor; Castle's Intrinsic Factor; Gastric Intrinsic Factor.

Внутренне Присущий Фактор

CAS — 9008-12-2.

Profile

Intrinsic factor, a glycoprotein secreted by the parietal glands in the stomach, is required for absorption of vitamin B_{12} in the small intestine. Deficiency in intrinsic factor leads to vitamin B_{12} deficiency disorders and pernicious anaemia.

Intrinsic factor is given orally with cyanocobalamin in the Schilling test in the differential diagnosis of pernicious anaemia (see p.1981). It is also included in some oral preparations containing cyanocobalamin, presumably as an aid to absorption.

◊ Difficulty in obtaining intrinsic factor and/or radio-labelled cyanocobalamin for the original Schilling test prompted studies using a recombinant human intrinsic factor in a new vitamin B_{12} absorption test. Initial results with this recombinant form were promising.[1]

1. Hvas A-M, *et al.* The effect of recombinant human intrinsic factor on the uptake of vitamin B12 in patients with evident vitamin B12 deficiency. *Haematologica* 2006; **91:** 805–8.

Preparations

Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Braz.:*** Hemofer†; ***Indon.:*** Biosanbe; ***Philipp.:*** TriHEMIC; ***USA:*** Anemagen†; Chromagen; Contrin; Ferotrinsic; Fetrin; Livitrinsic-f; Pronemia Hematinic; TriHEMIC; Trinsicon.

Inulin *(BAN)*

Alant Starch; Inulina.

CAS — 9005-80-5.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Inulin). A polysaccharide obtained from the tubers of *Dahlia variabilis*, *Helianthus tuberosus*, and other genera of the family Compositae. It is a white, odourless or almost odourless, hygroscopic, amorphous, granular powder. Slightly soluble in cold water, but freely soluble in hot water; slightly soluble in organic solvents.

USP 31 (Inulin). A polysaccharide which, on hydrolysis, yields mainly fructose. A white, friable, chalk-like, amorphous, odourless powder. Soluble in hot water; slightly soluble in cold water and in organic solvents. A 10% solution in water has a pH of 4.5 to 7.0. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Pharmacokinetics

Inulin is rapidly removed from the circulation after intravenous doses but is not metabolised. A trace may be found in the bile and may cross the placenta, but it is mainly eliminated in the urine by glomerular filtration without secretion or reabsorption in the renal tubule.

Uses and Administration

Inulin is used intravenously as a diagnostic agent to measure the glomerular filtration rate. Although an accurate test, it is complex to perform and is generally reserved for research purposes. Crystals of inulin may be deposited on storage of the injection; they should be dissolved by heating for not more than 15 minutes before use and the injection cooled to a suitable temperature before use.

Polyfructosan, an inulin analogue of lower average molecular weight, has been used similarly.

Preparations

BP 2008: Inulin Injection;
USP 31: Inulin in Sodium Chloride Injection.

Proprietary Preparations (details are given in Part 3)
Austria: Inutest; ***Cz.:*** Inutest†.

Multi-ingredient: ***Chile:*** Reduc-Te; Reducform-F; ***Fr.:*** Actyfilus; Effadiane relipidantes; ***Ital.:*** Enterolactis; Lactolas; Naturalass; Snell'it.

Iris Versicolor

Blue Flag; Iris Virginica.

Profile
The rhizomes of *Iris versicolor* (Iridaceae) are used in herbal preparations for skin and gastrointestinal disorders.

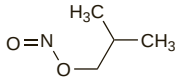
Homoeopathy. Iris versicolor has been used in homoeopathic medicines under the following names: Iris; Iris ver.

Preparations
Proprietary Preparations (details are given in Part 3)

Multi-ingredient: ***UK:*** Catarrh Mixture; HRI Clear Complexion; Skin Eruptions Mixture.

Isobutyl Nitrite

$C_4H_9NO_2$ = 103.1.
CAS — 542-56-3.



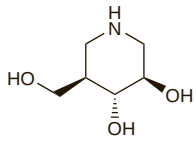
NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of isobutyl nitrite: Aroma of men; Bolt; Bullet; Climax; Hardware; Krypt tonight; Locker room; Poppers; Quicksilver; Rush; Rush Snappers; Snappers; Thrust; White out; Whiteout.

Profile
Isobutyl nitrite is not used medicinally but, as with other volatile nitrites, is abused for its vasodilating and related effects following inhalation (see Abuse, under Amyl Nitrite, p.1437).

Isofagomine

AT-2101 (tartrate). (3*R*,4*R*,5*R*)-3,4-Dihydroxy-5-(hydroxymethyl)piperidine.

$C_6H_{13}NO_3$ = 147.2.
CAS — 169105-89-9 (isofagomine); 161302-93-8 (isofagomine hydrochloride).



NOTE. The code AT-2101 has also been applied to a topical formulation of diclofenac in hyaluronic acid used in the treatment of actinic keratoses.

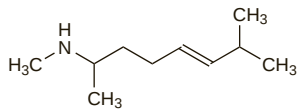
Profile
Isofagomine is an iminosugar under investigation as the tartrate for oral therapy of Gaucher disease (p.2249). It is a pharmacological chaperone that stabilises the variant lysosomal glucocerebrosidase facilitating its folding and transport from the endoplasmic reticulum into lysosomes, thereby increasing the pool of active endogenous enzyme.

Isometheptene Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de isometepteno; Isométheptène, Chlorhydrate d'; Isomethepteni Hydrochloridum. 1,5,*N*-Trimethylhex-4-enylamine hydrochloride; 1,5-Dimethylhex-4-enyl(methyl)amine hydrochloride.

Изометептена Гидрохлорид

$C_9H_{19}N$,HCl = 177.7.
CAS — 503-01-5 (isometheptene); 6168-86-1 (isometheptene hydrochloride).
ATC — A03AX10.
ATC Vet — QA03AX10.



(isometheptene)

Isometheptene Mucate *(BANM, rINNM)* ⊗

Isométheptène, Mucate d'; Isomethepteni Mucas; Mucato de isometepteno. Isometheptene galactarate.

Изометептена Мукат

$(C_9H_{19}N)_2,C_6H_{10}O_8$ = 492.6.
CAS — 7492-31-1.
ATC — A03AX10.
ATC Vet — QA03AX10.

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Isometheptene Mucate). A white crystalline powder. Very soluble in water; slightly soluble in dehydrated alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 5.4 to 6.6. Store in airtight containers. Protect from light.

USP 31 (Isometheptene Mucate). A white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a 5% solution in water is between 6.0 and 7.5.

Adverse Effects and Precautions
As for Sympathomimetics, p.1407.

Porphyria. Isometheptene mucate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions
As for Sympathomimetics, p.1407. Isometheptene has been reported to produce severe hypertensive reactions in patients receiving MAOIs.

Bromocriptine. For a report of hypertension and life-threatening complications after use of isometheptene and *bromocriptine*, see under Sympathomimetics, p.800.

Uses and Administration
Isometheptene is an indirect-acting sympathomimetic (p.1408). It is included for its vasoconstrictor effect, usually as the mucate, in some analgesic combination products used to treat acute migraine attacks (p.616). Typical oral doses of isometheptene mucate in migraine are 130 mg at the beginning of an attack, with 65 mg hourly thereafter as necessary, up to a total maximum dose of 325 mg in a 12-hour period.

Isometheptene hydrochloride has also been used in the management of migraine and smooth muscle spasm; it has been given orally, as well as by intramuscular, or occasionally subcutaneous, or slow intravenous, injection. The mucate has also been used in the management of muscle spasms.

Preparations
USP 31: Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules.

Proprietary Preparations (details are given in Part 3)
Turk.: Octinum.

Multi-ingredient: ***Braz.:*** Cefaldina; Doralgina; Doridina; Dorsedin; Migranette; Neomigran†; Neosaldina; Neuralgina; Sedalgina; Sedol; Tensaldin; ***Hong Kong:*** Midrid†; ***UK:*** Midrid; ***USA:*** Duradrin†; Midrin; MigraTen; Migratine†.

Isospaglumic Acid *(rINN)*

Acide Isospaglumique; Ácido isospaglúmico; Acidum Isospaglumicum; NAAGA. *N*-(*N*-Acetyl-L-α-aspartyl)-L-glutamic acid.

Изоспаглумовая Кислота

$C_{11}H_{16}N_2O_8$ = 304.3.
CAS — 3106-85-2.

Spaglumic Acid *(rINN)*

Acide Spaglumique; Ácido espaglúmico; Acidum Spaglumicum. *N*-(*N*-Acetyl-L-β-aspartyl)-L-glutamic acid.

Спаглумовая Кислота

CAS — 4910-46-7.
ATC — R01AC05; S01GX03.
ATC Vet — QR01AC05; QS01GX03.

Profile
N-Acetyl-L-aspartylglutamate is a mast cell stabiliser and has been used as the sodium or magnesium salts of spaglumic or isospaglumic acids in eye drops for allergic eye conditions and in nasal solutions for allergic rhinitis.

N-Acetyl-L-aspartylglutamate also has a role as a neurotransmitter and has been investigated in CNS disorders.

Preparations
Proprietary Preparations (details are given in Part 3)
Arg.: Naabak; ***Austria:*** Rhinaaxia; ***Braz.:*** Naabak; Naaxia; ***Chile:*** Alerbak; Naaxia; ***Cz.:*** Naaxia†; ***Fr.:*** Naabak; Naaxia; Naaxiafree; Rhinaaxia; ***Gr.:*** Rhinaaxia†; ***Hong Kong:*** Naaxia; ***Hung.:*** Naaxia; Rhinaaxia†; ***Ital.:*** Naaxia; Rhinaaxia; ***Philipp.:*** Naaxia; ***Port.:*** Naabak; Naaxia†; ***Singapore:*** Naabak; ***Spain:*** Naaxia; ***Switz.:*** Rhinaaxia†; ***Turk.:*** Naaxia; ***Venez.:*** Naabak.

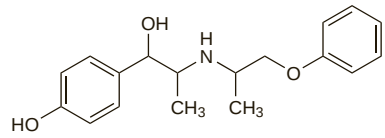
Multi-ingredient: ***Gr.:*** Naaxia; ***S.Afr.:*** Naaxia†; ***Switz.:*** Naaxia.

Isoxsuprine Hydrochloride *(BANM, rINNM)*

Caa-40; Hidrocloruro de isoxsuprina; Isoksupriinihydrokloridi; Isoxsuprin hydrochlorid; Isoxsuprine, chlorhydrate d'; Isoxsuprinhydroklorid; Isoxsuprini hydrochloridum; Izokssuprino hidrochloridas; Izoxszuprin-hidroklorid; Phenoxyisopropylnorsuprifen. 1-(4-Hydroxyphenyl)-2-(1-methyl-2-phenoxyethylamino)propan-1-ol hydrochloride.

Изоксуприна Гидрохлорид

$C_{18}H_{23}NO_3$,HCl = 337.8.
CAS — 395-28-8 (isoxsuprine); 579-56-6 (isoxsuprine hydrochloride).
ATC — C04AA01.
ATC Vet — QC04AA01.



(isoxsuprine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Isoxsuprine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 31 (Isoxsuprine Hydrochloride). A white, odourless, crystalline powder. Soluble 1 in 500 of water, 1 in 100 of alcohol and of 0.1N sodium hydroxide solution, and 1 in 2500 of 0.1N hydrochloric acid; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 6.0. Store in airtight containers.

Adverse Effects
Isoxsuprine may cause transient flushing, hypotension, tachycardia, rashes, and gastrointestinal disturbances. Maternal pulmonary oedema and fetal tachycardia have been reported after intravenous use in premature labour.

Pulmonary oedema. Pulmonary oedema has been reported in mothers given isoxsuprine for premature labour.[1,2]

1. Nagey DA, Crenshaw MC. Pulmonary complications of isoxsuprine therapy in the gravida. *Obstet Gynecol* 1982; **59** (suppl): 38S–42S.
2. Nimrod C, *et al*. Pulmonary edema associated with isoxsuprine therapy. *Am J Obstet Gynecol* 1984; **148:** 625–9.

Precautions
Isoxsuprine is contra-indicated after recent arterial haemorrhage. It should not be given immediately post partum, nor should it be used for premature labour if there is infection.

In women being treated for premature labour, the risk of pulmonary oedema means that extreme caution is required and the precautions and risk factors discussed under Salbutamol Sulfate, p.1132, apply.

Pregnancy. Ileus was found to be more common in the offspring of mothers who received isoxsuprine than in matched controls.[1] The incidence of respiratory distress syndrome also rose as the isoxsuprine concentration in cord blood exceeded 10 nanograms/mL; likewise the incidence of hypocalcaemia and hypotension rose progressively with increasing concentrations. The cord concentrations correlated inversely with the drug-free interval before delivery and it was suggested that with frequent assessment of uterine response it should be possible to avoid delivering infants at a time when they have high plasma-isoxsuprine concentrations.[1]

In another study[2] of the association between ruptured membranes, beta-adrenergic therapy, and respiratory distress syndrome, it was found that both therapy with isoxsuprine and premature rupture of membranes were individually associated with a lowered incidence of respiratory distress syndrome, but when present together they resulted in an increased risk of respiratory distress syndrome. It was suggested that therapy with beta-adrenergic drugs including isoxsuprine should be restricted to patients with intact membranes.[1]

1. Brazy JE, *et al*. Isoxsuprine in the perinatal period II: relationships between neonatal symptoms, drug exposure, and drug concentration at the time of birth. *J Pediatr* 1981; **98:** 146–51.
2. Curet LB, *et al*. Association between ruptured membranes, tocolytic therapy, and respiratory distress syndrome. *Am J Obstet Gynecol* 1984; **148:** 263–8.

Pharmacokinetics
Isoxsuprine hydrochloride is well absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 1 hour after an oral dose. A plasma half-life of about 1.5 hours has been reported. Isoxsuprine is excreted in the urine mainly as conjugates.

Uses and Administration
Isoxsuprine is a vasodilator that also stimulates beta-adrenergic receptors. It causes direct relaxation of vascular and uterine smooth muscle and its vasodilating action is greater on the arteries supplying skeletal muscles than on those supplying skin. Isox-