Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atridox 44 mg powder and solvent for gingival gel, pre-filled syringes

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe B contains doxycycline hyclate equivalent to 44 mg doxycycline.

After reconstitution: 502 mg of gel contains 44 mg doxycycline (8.8% w/w) as doxycycline hyclate.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for gingival gel.

Syringe A and Syringe B: Syringe A contains a colourless gel. Syringe B contains a yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For use in adults with chronic periodontitis at sites with probing depths of ≥ 5 mm, as an adjunct to conventional non-surgical management of periodontal disease.

4.2 Posology and method of administration

Gingival use.

Atridox is intended for adults and the elderly.

Atridox is not indicated for use in children and adolescents to 18 years of age.

Atridox should only be administered by dental care professionals.

The final blended product is 502 mg of formulation containing 44 mg of doxycycline (8.8% w/w doxycycline) and is sufficient material to treat up to sixteen sites with pocket depths averaging 6 mm.

Atridox is a variable dose product dependent on size, shape and number of pockets being treated. Atridox is intended for immediate use and for use in only one patient. Detailed instructions on administering the product are contained in section 6.6. Instructions for use and handling.

Following placement via a syringe, if necessary Atridox is packed into the pocket with a dental instrument until the pocket is completely filled with coagulated material.

Mechanical oral hygiene procedures other than brushing the occlusal surfaces of the dentition and the tongue should be avoided on all areas treated with Atridox for the first 7 days after treatment.

Following the initial application, if required, a second application may be used 4 months later.

4.3 Contraindications

Atridox is contraindicated in:

Hypersensitivity to doxycycline hyclate and any active substance in the tetracycline class or to any of the excipients.

Tooth development.

Pregnancy and lactation.

Patients on whom prophylactic antibiotics are to be administered prior to periodontal treatment.

Patients at risk of acute porphyria.

Patients with severe hepatic impairment.

Children and adolescents to 18 years of age.

4.4 Special warnings and precautions for use

Warnings

Tetracyclines as a class are associated with photosensitivity and may give an exaggerated sunburn reaction. Treatment should be discontinued at the first sign of cutaneous erythema.

Data from clinical trials have not established the use of Atridox in:

a. Patients with compromised heart conditions requiring subacute bacterial endocarditis (SBE) prophylaxis.

b. Patients with a history of rheumatic fever.

c. Patients who are HIV positive and/or with AIDS.

d. Patients taking medications that could cause gingival hyperplasia (e. g. phenytoin, cyclosporine, etc.) within one month of starting initial therapy.

e. Immunocompromised patients such as those receiving cancer therapy and/or radiation therapy, immunosuppressive therapy and rheumatic patients receiving anti-rheumatic therapy e. g. corticosteroids and non-steroidal anti-inflammatory drugs.

Precautions for use

Doxycycline compounds should be administered with caution to patients with hepatic impairments.

In patients with renal failure, tetracyclines may accumulate which may result in hepato-toxicity. These effects are unlikely to occur with Atridox in view of the low plasma concentrations of doxycycline.

In patients with a history of candidiasis, doxycycline may increase the potential for oral candidiasis.

As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi.

4.5 Interaction with other medicinal products and other forms of interaction

The systemic exposure of doxycycline after administration of Atridox is very low. Systemic interactions are unlikely to occur in view of the low plasma concentrations of doxycycline (≤ 0.1 μg/ml, see section 5.2.).

In case of combination of orally administered doxycycline with retinoids, intracranial hypertension may occur. The combination should therefore be avoided.

Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. Although these effects are unlikely to occur with Atridox because of low plasma concentrations of doxycycline, caution should be exercised.

4.6 Fertility, pregnancy and lactation

Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. The use of tetracyclines during tooth development may cause permanent discolouration of the teeth.

In animal studies, *N*-methyl-2-pyrrolidone has been associated with embryotoxicity and teratogenicity at maternally toxic doses.

Tetracyclines are present in the milk of breast-feeding women who are taking a drug of this kind and should therefore not be used in breast-feeding mothers.

Consequently, Atridox is contraindicated in pregnancy and lactation (See 4.3).

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Treatment related adverse events associated with the use of Atridox were no more serious nor frequent than events associated with standard periodontal treatments. In 3 Phase III clinical trials involving 609 patients, adverse events were reported with the following frequencies:

Organ system	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**
Infections and infestations		Acute periodontitis 0.4%; periapical abscess with sinus 0.3%; acute gingivitis 0.2%; oral aphthae 0.1%; pulpitis 0.1%
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Swelling, mass or lump in head and neck 0.1%
Nervous system disorders		Headache 0.3%

Gastrointestinal disorders		Glossodynia 0.3%; nausea and vomiting 0.3%; acute pharyngitis 0.1%; non-infectious gastroenteritis and colitis 0.1%; stomatitis 0.1%
Skin and subcutaneous tissue disorders		Disturbance of skin sensation 0.2%
General disorders and administration site conditions	Gum pain, increased probing depth 1.9%; tooth sensitivity (thermal) 1.1%	Oral pain, redness, erythema and trauma 0.5%; tooth ache, pressure sensitivity 0.3%; bleeding gums, ulceration 0.1%

The use of Atridox results in very low blood levels of doxycycline. Consequently, the majority of systemic complications of doxycycline are unlikely to occur. In post-marketing experience, administration of Atridox has rarely (≥1/10 000 to <1/1000) been associated with mild allergic reactions that manifest as swelling and/or inflammation around the site of placement or a more generalised rash. Melanoglossia (black tongue) has been described very rarely (< 1/10 000).

Oral administration of tetracycline has infrequently been associated with the following side effects which are not already mentioned above:

Gastro-intestinal: Anorexia, diarrhoea, inflammatory lesions (with monilial overgrowth) in the anogenital region. Oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline. A significant proportion of these cases has occurred with the hydrochloride salt in the capsule form. Most of these patients took medication immediately before going to bed.

Very rarely, dysphagia has been reported.

Respiratory: Hoarseness has been described very rarely.

Skin: Photosensitivity. In very rare cases with doxycycline therapy, severe skin reactions with life threatening reactions (exfoliative dermatitis, Lyell-syndrome (toxic epidermal necrolysis)) have been reported.

Renal toxicity: Rise in blood urea has been reported with tetracyclines and is apparently dose related.

Central nervous system: In very rare cases, increase of intracranial pressure (pseudotumour cerebri). The symptoms are headache, nausea, vomiting and visual disturbance caused by a papillary oedema.

Other: Hypersensitivity reactions (including urticaria and angioneurotic oedema), pericarditis and exacerbation of systemic lupus erythematosus have been reported. Severe acute hypersensitivity reactions have been very rarely described, including anaphylaxis and anaphylactoid purpura. Symptoms and signs include facial oedema, glossoncus (swollen tongue) and laryngeal oedema leading to life threatening narrowing of the airway; tachycardia, hypotension, shock and cardiac arrest may occur in this situation.

Blood: Haemolytic anaemia, thrombocytopenia, neutropenia and eosinophilia have been reported with tetracyclines.
When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur.

4.9 Overdose

Acute overdosage is not anticipated. In the event of overdosage, remove Atridox from the pockets, apply gastric lavage if appropriate and other supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives for local oral treatment
ATC code: A01AB22

Doxycycline is a broad-spectrum semisynthetic tetracycline that is more lipophilic than tetracycline. Doxycycline is bacteriostatic and inhibits bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites. *In vitro* testing has shown periodontal pathogens such as *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus,* and *Fusobacterium nucleatum* to be susceptible to 0.06 - 6.0 µg/ml doxycycline. A clinical study demonstrated that a single treatment with Atridox in patients with periodontal disease resulted in reduced levels of *Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus, Fusobacterium nucleatum, Bacteroides forsythus and Eikenella corrodens* in subgingival plaque. Levels of aerobic bacteria were also reduced.

Susceptible	**Minimum Inhibitory Concentrations (MIC90)**
Actinobacillus actinomycetemcomitans	6 µg/ml
Bacteroides forsythus	<6 µg/ml
Campylobacter rectus	1 µg/ml
Eikenella corrodens	6 µg/ml
Fusobacterium nucleatum	2 µg/ml
Porphyromonas gingivalis	1 µg/ml
Prevotella intermedia	3 µg/ml
Intermediate	Not applicable
Insusceptible	Not applicable

Cross-resistance between tetracyclines may develop in micro-organisms and patients may become cross-sensitised to tetracyclines.

Reported doxycycline *in vitro* MIC_{90} levels for suspected periodontal pathogens range from 1-6 µg/ml. The highest *in vitro* MIC_{90} levels are 32 µg/ml. *In vivo* doxycycline levels are initially 30-40 times the highest reported levels and at Day 7 post treatment are still 4-10 times these levels.

While the antibacterial activity of doxycycline is the principal therapeutic action in treating periodontitis the compound has other properties which are of value which may affect this condition. These include anti-collagenase properties, with those derived from neutrophils being most susceptible, anti-inflammatory activity and inhibition of bone resorption. These activities are thought to slow the progression of periodontitis.

5.2 Pharmacokinetic properties

Gingival and crevicular fluid, saliva and serum levels of doxycycline have been established following the administration of either Atridox or oral doxycycline.

Atridox when covered with a retentive material had initial mean gingival crevicular fluid levels of 1282-1500 µg/ml. After seven days levels were 152-317 µg/ml.

Studies indicate that ≥ 95% of the doxycycline will be released in the first 10 days following placement. Approximately 95% of the polymer will bioabsorb or be expelled from the pocket naturally in 28 days.

The maximum concentration of doxycycline in saliva two hours after Atridox treatment was 4.05 µg/ml and decreased to 0.36 µg/ml at the seventh day.

The concentration of doxycycline in serum following Atridox treatment never exceeded 0.1 µg/ml.

5.3 Preclinical safety data

Doxycycline, NMP (*N*-methyl-2-pyrrolidone) and PLA (Poly [DL-lactide]) have a low potential for acute toxicity in particular regard to the administration and dosage in question. (See points 4.8 and 4.9).

Doxycycline crosses the placenta. Furthermore, embryotoxicity, but not teratogenicity, has been reported. NMP is associated with embryotoxicity and teratogenicity in mice and rabbits at maternal toxic doses.

No data on mutagenicity of doxycycline and PLA have been submitted. NMP has been tested and the results do not indicate a mutagenic potential.

Subgingival administration of the doxycycline formulations in the dog results in transient slight irritation which quickly resolves. The constituents of the polymer formulation, PLA and NMP, and the polymer itself, have shown little or no increase in irritative potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poly (DL-lactide)
N-methyl-2 pyrrolidone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years in the pouch. For immediate use after reconstitution.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Interlocking disposable pre-filled syringes having PP barrels, PP collar, PE and PP caps and PP plungers with natural thermoplastic rubber tips. One carton contains 1, 2 or 6 pouches, each of which contains one pre-filled syringe A (450mg ATRIGEL delivery system), one pre-filled syringe B (44 mg doxycycline as doxycycline hyclate) and a blunt-ended cannula.

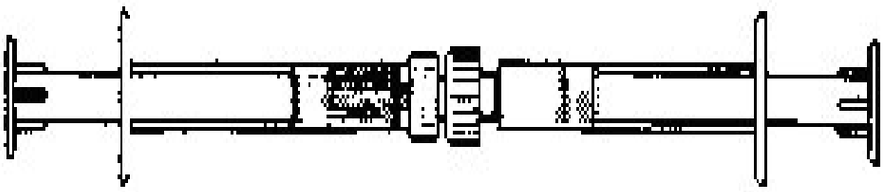
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each Atridox syringe system is intended for immediate use and for use only in one patient. Do not use if the pouch has been previously opened or damaged.

1. Couple Syringe A (liquid delivery system) and Syringe B (drug powder).

Syringe A **Syringe B**

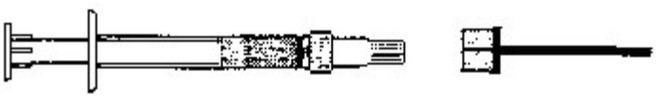


2. Inject the liquid contents of Syringe A (indicated on syringe by teal stripe) into Syringe B (doxycycline powder) and then push the contents back into Syringe A. This entire operation is one mixing cycle.

3. Complete 100 mixing cycles at a pace of one cycle per second using brisk strokes.

4. The contents will be in **Syringe A** (indicated by teal stripe). Hold the coupled syringes vertically with **Syringe A** at the bottom. Pull back on the **Syringe A** plunger and allow the contents to flow down the barrel for several seconds. An opaque ring may be observed after constitution. However, if additional unmixed drug powder is evident, or if seepage of the formulation outside of the barrels is observed, discard the coupled syringes.

5. Uncouple the two syringes and attach the blunt-ended cannula to Syringe A.



Syringe A **Blunt Cannula**

Product is now ready for application

Atridox does not require local anaesthesia for placement. Bend the cannula to resemble a periodontal probe and explore the periodontal pocket in a manner similar to periodontal probing. Keeping the cannula tip near the base of the pocket, express the product into the pocket until the polymer reaches the top of the gingival margin. Withdraw the cannula tip from the pocket. In order to separate the tip from the polymer, turn the tip of the cannula towards the tooth, press the tip against the tooth surface, and pinch the string of polymer from the tip of the cannula. Variations on this technique may be needed to achieve separation between Atridox and cannula.

When necessary, using an appropriate dental instrument, pack the Atridox into the pocket. Dipping the edge of the instrument in water before packing will help keep Atridox from sticking to the instrument, and will help speed coagulation of Atridox. A few drops of water dripped onto the surface of Atridox once in the pocket will also aid coagulation. If necessary, add more Atridox as described above until the pocket is full.

For single use only.

Discard any excess after use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 1501/1/1

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10 DATE OF REVISION OF THE TEXT

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