ANNEX 1

SUMMARY OF PRODUCT CHARACTERISTICS

1 - NAME OF THE MEDICINAL PRODUCT

AMIKACIN AGUETTANT 250 mg, powder for injectable solution.

2 - QUALITATIVE AND QUANTITATIVE COMPOSITION

Amikacin sulphate
Quantity corresponding to amikacin base ..... 250.0 mg

Sodium hydroxide or sulphuric acid .....q.s. to pH = 6.8

per vial

3- PHARMACEUTICAL FORM

Powder for injectable solution.

4- CLINICAL PARTICULARS

4.1 Therapeutic indications

The indications are given by the antibacterial activity and pharmacokinetic characteristics of amikacin.
They take account both of the clinical trials undergone by the drug and its place in the spectrum of currently available antibacterial products.

- When used as monotherapy, the indications are confined to infections by Gram-negative bacilli defined as sensitive to amikacin, particularly renal and urological infections.

- Combination of amikacin with another antibiotic may be justifiable in certain infections by sensitive organisms, on the basis of bacteriological data, particularly in the case of:
  - . renal, urological and genital infections,
  - . septicaemia and endocarditis,
  - . meningeal infections (in combination with local treatment),
  - . respiratory infections,
  - . cutaneous infections (cutaneous staphylococcal infection of the face),
  - . articular infections.

It is advisable to take account of official recommendations concerning the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

* In persons with normal renal function.

Intramuscular route

. Adults and children:
15 mg/kg/day, which may be given in divided doses as:
- 15 mg/kg once a day
- 7.5mg/kg twice a day
- 5 mg/kg three times a day

. Babies:
15 mg/kg/day, with monitoring of serum antibiotic levels.
In cases of uncomplicated urinary infection, the dosage may be halved.

Intravenous route (slow intravenous infusion)

- Amikacin must not be given by direct intravenous injection.
- Amikacin must be diluted in sodium chloride solution or isotonic dextrose solution at a concentration of 500 mg per 200 ml of solution.
- The infusion must be given over a period of 30 minutes to one hour.

. Adults and children:
The daily dose is the same as when given by the intramuscular route. Once again, it can be divided into 2 or 3 separate infusions.

. Babies and neonates:
15 mg/kg/day, with monitoring of serum antibiotic levels.
Since the aminoglycosides first became available, it has been demonstrated that it is possible to reduce the number of daily doses while maintaining the same total daily dosage. Traditionally, three injections have been given daily, particularly when giving maximum doses; sometimes 2 daily doses have been given. Experience now available suggests that the appropriate number of daily doses is either 2 or a single one.
The daily dose can be given as a single daily injection (i.m., or as a short infusion) :
- in patients aged under 65 years
- with normal renal function,
- when treatment does not exceed 10 days,
- in the absence of neutropenia
- other than when treating Gram-positive organisms
- for Gram-negative bacterial infections other than *Pseudomonas* or *Serratia*.

Under the above circumstances, a single daily injection has been shown to have at least identical efficacy and to be sometimes better tolerated than classical (8-hourly) treatment schedules.

In other cases, twice-daily administration of the usual dose is most commonly recommended, other than in renal failure which demands the use of traditional measures.

Plasma antibiotic assays are useful when treatment is to be given for longer than 7 to 10 days. A trough level below 5 µg/ml indicates that the treatment schedule chosen is appropriate for the patient's clearance capacity.

In extremely serious infections, the daily dosage may exceptionally be escalated to 1.50 g in adults. Monitoring of renal and auditory function must be intensified.

In general terms, the total dose per treatment course should not exceed 15 g.

Subcutaneous administration

Amikacin can be administered by the subcutaneous route at the same dosage as for the intramuscular route.

Intrathecal administration

Amikacin can be given intrathecally at a dose of 0.5 mg/kg, one injection every 48 hours, repeated 3 to 4 times after sterilisation of the cerebrospinal fluid.

* Patients with renal failure

It is essential to adjust the dosage, to carry out regular monitoring of renal, cochlear and vestibular function, and to perform check serum antibiotic assays as frequently as possible.

Measurements of the serum creatinine level or of endogenous creatinine clearance are the best tests for assessing renal function and adjusting dosage accordingly.

In practice, an initial loading dose of 7.5 mg/kg should be given, and subsequently repeated bearing in mind that the time T' between successive injections must equal 3 T½, the value of T½ being given by the equation:

$$T½ \text{ (hours)} = 0.3 \times Cr \text{ (mg/litre)}$$

For example, for a serum creatinine (Cr) of 40 mg/litre:

$$T½ \text{ (hours)} = 0.3 \times 40 = 12 \text{ hours}$$
$$T' = 3\ T½ = 3 \times 12 = 36 \text{ hours}$$

If T' is greater than 40 hours, the schedule should be changed and half the dose should be given every T½.

* Patients on haemodialysis

Following a loading dose of 5 to 7.5 mg/kg, the doses to be given should be determined after each dialysis session, taking account of the measured serum concentrations.

Method of administration

Dissolve the contents of a 250 mg vial in the 2 ml contained in the ampoule of Water for injections.
The reconstituted solution may be slightly tinged with yellow. This does not indicate any loss of activity of the product.

Intravenous infusion
The following solutions may be used, dissolving 500 mg of amikacin per 200 ml of solution:
. isotonic (0.9%) sodium chloride solution
. isotonic (5 %) dextrose solution
. 10 % dextrose solution

4.3 Contraindications

This drug must never be used in the following cases:
. allergy to antibiotics of the aminoglycoside class
. myasthenia gravis.
- Concurrent administration of another aminoglycoside is contraindicated.
- This medicament should generally not be given in combination with polymyxin by the parenteral route, or with botulinum toxin (cf. section "Interaction with other medicinal products").
- The use of this medicament is generally contraindicated during pregnancy.
- Lactation is not advisable while this medicament is being taken.

4.4 Special warnings and special precautions for use

- The nephrotoxicity and ototoxicity of amikacin necessitate the following precautions for use:

. In patients with renal failure, amikacin should only be used when strictly necessary, and the dosage should be adjusted in the light of the creatinine clearance (cf. "Posology and method of administration"). Medical supervision of renal and auditory function is necessary. Serum antibiotic levels must be monitored as closely as possible.

. In view of the pharmacokinetics of the product and the mechanisms of its ototoxicity and nephrotoxicity, repeated and/or prolonged administration should be avoided, particularly in elderly subjects.

. Amikacin should not be given in combination with highly active diuretics, or with any other ototoxic or nephrotoxic compounds.

- Amikacin must be used with caution in patients with abnormalities of the vestibular or cochlear systems.

- If the patient is to undergo any surgical procedure, the anaesthetist must be informed that the patient is receiving amikacin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Associations that are contraindicated

. Concurrently administered aminoglycosides: increased risks of nephrotoxicity and ototoxicity.

Associations that are not recommended

. Polymyxin (parenteral): additive nephrotoxic effects. Not to be used in association except under strict supervision and with an unequivocal bacteriological justification.

. Botulinum toxin: risk of aggravation of the effects of botulinum toxin by aminoglycosides (by extrapolation from the observed effects during botulism). A different antibiotic should be used.

Associations necessitating precautions for use

. Cephalothin: the possibility has been raised that the nephrotoxicity of aminoglycosides may be increased by cephalothin.

Monitoring of renal function:

. Curare-like drugs: potentiation of curare-like drugs when the antibiotic is administered by the parenteral route before, during or after the curarising agent.

The degree of curarisation must be monitored at the end of anaesthesia.

. Loop diuretics (bumetanide and frusemide): increased risk of nephrotoxicity and ototoxicity from aminoglycosides (functional renal failure associated with the dehydration brought about by the diuretic).

The drugs can be given in association provided the patient's hydration, renal and cochleo-vestibular function are monitored, and if possible plasma aminoglycoside concentrations are also measured.

Associations to be taken into account

. Aminoglycosides administered sequentially: the risk of cumulative ototoxicity must be borne in mind (local or systemic administration).

. Amphotericin B: increased risk of nephrotoxicity.

. Ciclosporin: greater rise in serum creatinine than on ciclosporin alone (synergy of nephrotoxic effects of the two compounds).

. Cisplatin: additive nephrotoxic and ototoxic effects.

Special problems: derangement of the INR

There have been numerous reports of increased activity of oral anticoagulants in patients receiving antibiotics. Apparent risk factors include the associated clinical picture of marked infection or inflammation, and the patient's age and general condition. Under these circumstances it appears difficult to apportion responsibility for the derangement of the INR, as between the infectious pathology and its treatment. However, certain classes of antibiotics have been more particularly implicated: these include in particular the fluoroquinolones, macrolides, cyclines, co-trimoxazole and certain cephalosporins.

4.6 Pregnancy and lactation

Pregnancy

Studies in animals have demonstrated damage to the cochleo-vestibular apparatus and to renal function in several species.
In clinical practice, some cases of cochleo-vestibular damage have been described with certain aminoglycosides.
For these reasons the use of this medicament is not recommended during pregnancy. This consideration does not constitute a systematic argument in favour of termination of pregnancy, but represents a counsel of caution. If the use of a systemic aminoglycoside appears essential, the dosage should be adjusted in the light of the patient's weight and renal function.

Lactation

The degree to which aminoglycosides are secreted into breast milk is not well known but is probably low. Absorption of these compounds by the neonate's digestive tract is regarded as negligible.
The presence of these compounds in the neonate's intestine may bring about destruction of the digestive flora and the development of candidiasis or diarrhoea. The ototoxicity and nephrotoxicity of the aminoglycosides constitute a potential additional risk factor. For these reasons, breast-feeding is not recommended for women to whom this medicament is prescribed.

4.7 Effects on ability to drive and use machines

4.8 Undesirable effects

- Nephrotoxicity: this medicament is a member of the class of aminoglycosides, for which cases of renal failure have been reported. In most cases this complication was related to excessively high dosage or prolonged treatment, prior renal damage, haemodynamic disorders, or administration in combination with nephrotoxic compounds.
- Ototoxicity: this medicament is a member of the class of aminoglycosides, for which cases of cochleo-vestibular damage have been reported. This complication was favoured by excessively high dosage, prolonged treatment, pre-existing renal failure, or administration in combination with ototoxic compounds.
- Minor allergic reactions (rashes, urticaria) have been described. These complications resolved when treatment was stopped.

4.9 Overdose

In case of overdosage or toxic reactions, haemodialysis or peritoneal dialysis will accelerate the elimination of amikacin.

5- PHARMACOLOGICAL PROPERTIES

ANTIBACTERIAL ANTIBIOTICS of the aminoglycoside class
(J: anti-infectious agents)

5.1 Pharmacodynamic properties

Spectrum of antibacterial activity

Critical concentrations separate sensitive strains from strains of intermediate sensitivity, and these latter from resistant strains:
S ≤ 8 mg/l, and R > 16 mg/l

The prevalence of acquired resistance may vary depending on geography and weather in the case of certain species. It is therefore helpful to possess information about the prevalence of local resistance, particularly for the treatment of severe infections. Such data can do no more than provide a guide to the probability of a particular bacterial strain's being sensitive to this antibiotic.
Where the variability of the prevalence of resistance in France is known for a bacterial species, this is shown in the table below:

Categories	**Frequency of acquired resistance in France (> 10 %) (extreme values)**
SENSITIVE SPECIES	
Gram-positive aerobes	
Corynebacterium	
Listeria monocytogenes	
Nocardia asteroides	
Staphylococcus, methicillin-sensitive	
Gram-negative aerobes	
Acinetobacter (primarily Acinetobacter baumannii)	
Branhamella catarrhalis	
Campylobacter	
Citrobacter freundii	
Citrobacter koseri	
Enterobacter aerogenes	20 – 40 %
Enterobacter cloacae	
Escherichia coli	
Haemophilus influenzae	
Klebsiella	0 - 20 %
Morganella morganii	
Proteus mirabilis	
Proteus vulgaris	
Providencia rettgerii	
Providencia stuartii	
Pseudomonas aeruginosa	5 – 20 %
Salmonella	
Serratia	5 – 15 %
Shigella	
Yersinia	

Categories	Frequency of acquired resistance in France (> 10 %) (extreme values)
Other	
Mycobacteria	
MODERATELY SENSITIVE SPECIES	
(intermediate sensitivity in vitro)	
Gram-negative aerobes	
Pasteurella	
RESISTANT SPECIES	
Gram-positive aerobes	
*Enterococci**	
*Staphylococcus, methicillin-resistant***	
Gram-negative aerobes	
Alcaligenes denitrificans	
Burkholderia	
Flavobacterium sp.	
Stenotrophomonas maltophila	
Streptococcus	
Anaerobes	
Strict anaerobes	
Other	
Chlamydia	
Myocoplasma	
Rickettsia	

* For certain indications, amikacin can be used in combination, particularly with beta-lactam antibiotics (e.g. septicaemia, endocarditis). However, synergy is abolished if the species involved (e.g. Streptococcus, Enterococcus) show high-grade acquired resistance to amikacin (30 - 80% of strains).

** The frequency of methicillin resistance is around 30 - 50% of all Staphylococci; resistant strains are mainly encountered in a hospital environment.

5.2 Pharmacokinetic properties

Distribution

Intramuscular administration:
- in subjects with normal renal function, an i.m. injection of 7.5 mg/kg (500 mg in an adult) produces a peak serum level of 20 µg/ml after one hour.

Intravenous administration
- in subjects with normal renal function, a dose of 7.5 mg/kg given as a 30-minute i.v. infusion produces a serum level of 38 µg/ml at the end of the infusion.

- in healthy volunteers, the administration of a dose of 15 mg/kg as a continuous i.v. infusion over 30 minutes produces serum levels of approximately 77 µg/ml at the end of the infusion, and of 47 and 1 µg/ml after one hour and 12 hours respectively.

- in elderly subjects with a mean creatinine clearance of 64 ml/min, the administration of a dose of 15 mg/kg as a continuous i.v. infusion over 30 minutes produces serum levels of 55 µg/ml at the end of the infusion, and of 5.4 µg/ml and 1.3 µg/ml after 12 hours and 24 hours respectively.

In studies using repeated doses, no cumulation was demonstrated in subjects with normal renal function who received single or daily doses of 15 to 20 mg/kg.

. The mean half-life is 2 hours.
. The apparent distribution volume is 24 litres, or 28% of body weight.
. After parenteral injection, amikacin diffuses rapidly through the body:
. Approximately 10 to 20% of the serum concentration passes through healthy meninges; the proportion may reach 50% when the meninges are inflamed.
. Amikacin is also found at therapeutic concentrations in the peritoneal cavity, the pleural fluid and bronchial secretions (10 to 20% of serum concentrations).
. There is significant diffusion across the placental barrier. Concentrations of up to 20% of the maternal serum concentration have been found in fetal blood and amniotic fluid.
. Protein binding is less than 10%.

Excretion

- Amikacin is essentially excreted by the renal route, in its active form (by glomerular filtration). Over 90% of an injected dose is recovered in the urine within 24 hours. After a dose of 7.5 mg/kg, a urinary concentration of about 800 µg/ml is obtained in the first 6 hours' urine.

- In parallel with this urinary elimination there is also a low degree of elimination via the bile.

5.3 Preclinical safety data

6- PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities

It is not advisable to mix amikacin with other medicaments in the same syringe or infusion bottle.

6.2 Shelf life

2 years.

6.3 Special precautions for storage

Do not store above 25°C. Protect from light.

The reconstituted solution is stable for 12 hours at temperatures below 25 °C, or 10 days at a temperature of between 2 ° and 8 °C (in a refrigerator).

When given as an intravenous infusion, AMIKACIN AGUETTANT is stable for 24 hours in sodium chloride or dextrose (5% or 10%) solution.

6.4 Nature and contents of container

- Powder in 7 ml vial of plain type II glass with stopper (chlorobutyl), sealed with an aluminium capsule; box of 1.
- Powder in 7 ml vial of plain type II glass with stopper (chlorobutyl), sealed with an aluminium capsule; box of 10.
- Powder in 7 ml vial of plain type II glass with stopper (chlorobutyl), sealed with an aluminium capsule; box of 20.
- Powder in 7 ml vial of plain type II glass with stopper (chlorobutyl), sealed with an aluminium capsule; box of 50.

6.5 Instructions for use and handling

7- PRESENTATION AND ADMINISTRATIVE IDENTIFICATION NUMBER

560 363-1 : powder in vial (glass) ; box of 1
560 364-8 : powder in vial (glass) ; box of 10
560 365-4 : powder in vial (glass) ; box of 20
560 366-0 : powder in vial (glass) ; box of 50

8- LEGAL CATEGORY

List I.
Reserved for hospital use.

9- MARKETING AUTHORISATION HOLDER

Laboratoires AGUETTANT
1, rue Alexander Fleming
69007 LYON

10- DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MA: 14 March 1997
Amendments dated 27 October 1998, 11 September 2000