NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Gentamicin Injection BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL Gentamicin Injection BP contains Gentamicin sulfate BP equivalent to gentamicin base 10 mg or 40 mg per mL.

Excipient(s) with known effect

Each vial of DBL Gentamicin Injection BP contains sodium methyl hydroxybenzoate (2.06 mg/mL) and sodium propyl hydroxybenzoate (0.225 mg/mL) as preservative.

Each vial of DBL Gentamicin Injection BP contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

Also refer to Section 4.4, Excipients Information.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL Gentamicin Injection BP is a sterile solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Gentamicin Injection BP is indicated in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa
Proteus species (indole positive and indole negative)
Escherichia coli
Klebsiella - Enterobacter - Serratia species
*Staphylococcu*s species (coagulase positive and coagulase negative)

DBL Gentamicin Injection BP should be considered for the treatment of the following conditions when caused by susceptible organisms:

Septicaemia

Respiratory tract infections

Infected wounds, bone and soft tissue infections including peritonitis, septic abortion and burns complicated by sepsis

Urinary tract infections (recurrent, complicated)

DBL Gentamicin Injection BP is not routinely indicated in the initial treatment of uncomplicated urinary tract infections unless the organism is resistant to other less toxic antibacterials.

DBL Gentamicin Injection BP may be considered as initial therapy in suspected or confirmed gram negative infections and therapy may be instituted before obtained results of susceptibility testing. If anaerobic organisms are suspected, additional antimicrobial therapy should be added to the gentamicin regime.

The decision to continue therapy with gentamicin should be based on the results of susceptibility tests, the severity of the infection, and the important additional considerations outlined in section 4.4. If the causative organisms are resistant to gentamicin and the patient is not responding favourably, other appropriate therapy should be instituted.

4.2 Dose and method of administration

Dosage in patients with normal renal function

Adults

Type of Infection	Dosage	Dosage Interval	Duration of Therapy
Systemic & severe urinary tract infections* such as pyelonephritis	3 mg/kg/day (bodyweight > 60 kg: Usual individual dose 80 mg; bodyweight < 60 kg: usual individual dose 60 mg)	8 hours	7-10 days
Life threatening infections	5 mg/kg/day initially then 3 mg/kg/day as soon as clinically indicated	6-8 hours	7-10 days Longer therapy may be required. If so, auditory renal and vestibular functions should be monitored.

*Note: Gentamicin activity is increased at pH 7.5. It may therefore be advantageous to alkalinise the patient's urine before therapy.

Paediatric

Type of Infection	Age	Dosage #	Dosage Interval
Systemic	0 - 7 days 1 week - 1 year 1 year - 12 years	5 mg/kg/day initially 6 mg/kg/day initially 4.5 mg/kg/day initially	12 hours 12 hours 8 hours
Uncomplicated Urinary tract infections	-	3 mg/kg/day	8 – 12 hours
Life threatening infections	0 - 7 days 1 week - 1 year	5 mg/kg/day initially 7.5 mg/kg/day initially	12 hours 8 hours

Type of Infection	Age	Dosage #	Dosage Interval
	1 year - 12 years	6 mg/kg/day initially	8 hours

#Note: In neonates, infants and children, where possible, serum levels should be determined and the dose adjusted to provide the desired serum level.

Dosage in patients with impaired renal function

In the presence of renal failure it is particularly important to monitor renal, auditory and vestibular functions during gentamicin therapy. Dosage should be adjusted for patients with renal impairment to minimise the risk of toxicity. The first dose should be as normal; subsequent doses should be given less frequently, depending on the degree of renal impairment. Table 3 below provides guidelines for adjustment of the dosage interval based on renal function tests.

Creatinine Clearance (mL/minute)	Serum creatinine (mmol/litre)	BUN (mmol/litre)	Dosage interval
over 70	less than 0.12	less than 6.5	8 hours
35 – 70	0.12 - 0.17	6.5 - 10	12 hours
24 – 34	0.18 - 0.25	11 - 14	18 hours
16 – 23	0.26 - 0.33	15 - 18	24 hours
10 – 15	0.34 - 0.47	19 - 26	36 hours
5 – 9	0.48 - 0.64	27 - 36	48 hours

In adults with renal failure undergoing haemodialysis, the amount of gentamicin removed from the blood may vary depending upon several factors including the dialysis method used. An eight-hour haemodialysis may reduce serum concentrations of gentamicin by approximately 50%. The recommended dosage at the end of each dialysis period is 1 to 1.7 mg/kg depending upon the severity of infection.

The above dosage schedules are provided as guidelines only, and are not intended as a rigid dosage recommendations. The measurement of gentamicin serum levels is highly desirable in patients with renal impairment to ensure optimal serum gentamicin concentrations.

Bodyweight

Prior to administration, the patient's bodyweight should be measured for the correct calculation of dosage. In obese patients, the appropriate dose can be calculated by assuming the bodyweight is the patient's estimated lean bodyweight plus 40% of the excess.

Method of administration

DBL Gentamicin Injection BP is given by the intramuscular (IM) or intravenous (I.V) route when I.M. administration is not feasible, e.g. in shocked or severely burned patients. The dosage is the same for either route of administration (see above).

Whenever possible, and especially in patients with impaired renal function, peak and trough gentamicin serum concentrations should be determined and dosage adjusted where necessary, to maintain desired serum concentrations. In general, desired peak concentrations are between

4 and 10 micrograms/mL, and trough concentrations are below 2 micrograms/mL. Prolonged concentrations greater than these values may be associated with an increased risk of toxicity.

Blood specimens for the determination of peak gentamicin concentrations should be obtained approximately one hour following I.M. administration and 30 minutes after completion of a 30 minute infusion. Blood specimens for the trough gentamicin concentration should be obtained immediately prior to the next I.M. or I.V. dose.

Intravenous administration

For IV administration, the prescribed dose of gentamicin may be diluted in 100 to 200 mL of sterile normal saline or 5% glucose in water. The concentration of gentamicin in the solution should not exceed 1 mg/mL. Infusion periods of 30 minutes to 2 hours have been advocated.

Administration of the dose by bolus injection produces serum levels which are initially in excess of what is regarded as being safe from toxic side effects. The high serum level does however rapidly fall and the potential danger or safety of this method of administration is yet to be established.

DBL Gentamicin Injection BP must not be physically mixed with other drugs, but should be administered by separate infusion (see section 4.5).

DBL Gentamicin Injection BP is available in ampoules. Ampoules of the injection do not contain any bacteriostat and should be discarded following a single use.

4.3 Contraindications

Gentamicin is contraindicated in patients with

- a history of hypersensitivity to gentamicin, other aminoglycoside or any constituents of the injection (see section 6.1), as well as in patients who have experienced serious toxic reactions (ototoxicity or nephrotoxicity) to gentamicin or to other aminoglycoside therapy
- myasthenia gravis.

4.4 Special warnings and precautions for use

Gentamicin, as with other aminoglycosides, is potentially nephrotoxic and ototoxic.

Neurotoxicity

Neurotoxicity may be manifested by both vestibular and auditory ototoxicity. These auditory changes are generally irreversible, usually bilateral and may be partial or total. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. The risk of this toxicity is higher in patients receiving high doses, prolonged treatment, or with impaired renal function. Gentamicin should therefore be used with caution in patients with impaired renal function. In such patients the frequency of administration should be reduced and renal function should be monitored. Prolonged concentrations above 10 microgram/mL should be avoided and trough concentrations should not exceed 2 microgram/mL. In neonates, infants and children, dosage reductions may also be necessary to avoid toxicity.

Diabetes, auditory vestibular dysfunctions, previous use of ototoxic drugs and a genetically determined high sensitivity to aminoglycoside-induced ototoxicity, are other main factors which may predispose the patient to ototoxicity.

Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range. In case of family history of aminoglycoside induced deafness or known mitochondrial DNA mutations in the 12S rRNA gene, alternative treatments other than aminoglycosides should be considered.

Renal and eighth cranial nerve function should be closely monitored, especially in patients with known or suspected reduced renal function at onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Urine should be examined for decreased specific gravity, increased excretion of protein, and the presence of cells or casts. Blood urea nitrogen, serum creatinine, or creatinine clearance should be determined periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears or hearing loss) or nephrotoxicity requires dosage adjustment or discontinuance of the drug. As with the other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy. Treatment period should not normally exceed 10-14 days.

Serum concentrations of aminoglycosides should be monitored to assure adequate levels and to avoid potentially toxic levels. When monitoring gentamicin peak concentrations, dosage should be adjusted so that prolonged levels above 10 micrograms/mL are avoided. When monitoring gentamicin trough concentrations, dosage should be adjusted so that levels above 2 micrograms/mL are avoided. Excessive peak and/or trough serum concentrations of aminoglycosides may increase the risk of renal and eighth cranial nerve toxicity. In the event of overdose or toxic reactions, haemodialysis may aid in the removal of gentamicin from the blood, especially if renal function is or becomes compromised. The rate of removal of gentamicin is considerably less by peritoneal dialysis than by haemodialysis.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs can increase the possibility of gentamicin toxicity, (see section 4.5). Co-administration with the following agents should be avoided:

- neuromuscular blocking agents such as suxamethonium and tubocurarine
- other potentially nephrotoxic or ototoxic drugs such as cephalosporins
- potent diuretics such as etacrynic acid and furosemide
- other aminoglycosides
- amphotericin B
- cisplatin
- ciclosporin.

Other factors which may increase the risk of toxicity are dehydration, advancing age and diabetes mellitis. Patients should be well hydrated during therapy.

Patients treated with aminoglycoside antibiotics, including gentamicin, by injection, irrigation or local application, should be under close clinical observation because these drugs have the

inherent potential for causing neurotoxicity and nephrotoxicity, particularly if patients have pre-existing renal damage or if the drug is administered for longer periods or at higher doses than those recommended.

Recent evidence suggests that neurotoxic and nephrotoxic antibiotics may be absorbed in significant quantities from body surfaces after local irrigation or application. The potential toxic effect of antibiotics administered in this fashion should be considered and inadvertent contact with the skin should be removed with water.

Neuromuscular disorders

Aminoglycosides, including gentamicin, should be used with caution in patients with muscular disorders, such as myasthenia gravis or parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effect on neuromuscular junction.

Gentamicin should be used with care in conditions characterised by muscular weakness. Gentamicin induced renal tubular dysfunction including Fanconi syndrome acquired and Pseudo Bartter syndrome, with acid base and electrolyte disturbances has been reported in some infants, children and adults being given gentamicin injections. Muscle weakness, paraesthesias, tetany, positive Chvostek and Trousseau signs have been described in patients with hypomagnesemia, hypocalcaemia and hypokalaemia. All required appropriate corrective electrolyte therapy.

Use during anaesthesia

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of gentamicin (40 mg/kg). The possibility that prolonged or secondary apnoea may occur should be considered if the drug is administered to anaesthetised patients who are also receiving neuromuscular blocking agents such as suxamethonium, tubocurarine or decamethonium or in patients receiving massive transfusions of citrated blood. If neuromuscular blockade occurs it may be reversed by the administration of calcium salts.

Superinfection

Treatment with gentamicin may lead to an over-growth of non-susceptible organisms. If overgrowth of non-susceptible organisms occurs, appropriate therapy should be initiated.

Allergic reactions

May occur after administration of gentamicin. Cross allergenicity among aminoglycosides has been known to occur.

Excipient information:

As this product contains sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate, it may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm.

DBL Gentamicin Injection BP contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Obesity

In cases of significant obesity, gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered (see Section 4.2 Dose and method of administration).

Clostridioides difficile-associated diarrhoea

Clostridioides difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including gentamicin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C difficile*.

C difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Use in renal impairment

Gentamicin should be used with caution generally in premature infants because of their renal immaturity, in elderly people and generally in patients with impaired renal function. In some patients with impaired renal function, there has been a transient rise in blood urea nitrogen, which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of renal function.

Use in the elderly

Because of its toxicity, gentamicin should be used with caution in elderly patients only after less toxic alternatives have been considered and/or found ineffective. Elderly patients are more likely to have an age-related decrease in renal function. This may not be evident in the results of routine screening test such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Recommended doses should not be exceeded, and the patient's renal function should be carefully monitored during therapy. Elderly patients may require smaller daily doses of gentamicin in accordance with their increased age, decreased renal function, and possibly, decreased weight. In addition, loss of hearing may result even in patients with normal renal function.

Paediatric use

Gentamicin should be used with caution in premature and neonatal infants because their renal immaturity may result in the prolongation of the serum half-life of the drug and subsequent gentamicin induced toxicity.

Effects on laboratory tests

Laboratory abnormalities possibly related to gentamicin include: increased levels of serum transaminase (ALT, AST) serum LDH and bilirubin; decreased serum calcium, magnesium, sodium and potassium; anaemia, leukopenia, granulocytopenia, transient agranulocytosis, eosinophilia, increased and decreased reticulocyte counts, and thrombocytopenia. While clinical laboratory test abnormalities may be isolated findings, they may also be associated with clinically related signs and symptoms. For example, tetany and muscle weakness may be associated with hypomagnesaemia, hypocalcaemia and hypokalaemia.

4.5 Interaction with other medicines and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Co-administration with the following agents should be avoided:

- neuromuscular blocking agents such as suxamethonium and tubocurarine
- other potentially nephrotoxic or ototoxic drugs such as cephalosporins
- potent diuretics such as etacrynic acid and furosemide
- other aminoglycosides
- amphotericin B
- cisplatin
- ciclosporin (see Section 4.4 Special warnings and precautions for use).

Digoxin

Digoxin: Gentamicin has been known to increase serum digoxin levels.

Neuromuscular blocking agents or medications with neuromuscular blocking activity

Concurrent use of gentamicin with agents with neuromuscular blocking activity e.g. suxamethonium, tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics, opioid analgesics and massive transfusions with citrated anticoagulated blood, should be carefully monitored; neuromuscular blockade may be enhanced, resulting in skeletal muscle weakness and respiratory depression or paralysis (apnoea); caution is recommended when these medications and gentamicin are used concurrently during surgery or in the postoperative period, especially if there is a possibility of incomplete reversal of neuromuscular blockade postoperatively; treatment with anticholinesterase agents or calcium salts may help reverse the blockade.

Concurrent use of the botulinum toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Other neurotoxic and/or nephrotoxic agents

If possible, avoid concurrent or sequential use of other neurotoxic and/or nephrotoxic antibiotics, including other aminoglycosides, polymyxin B, colistin, vancomycin, amphotericin B, clindamycin, and cephalosporins; cisplatin and ciclosporin.

Any potential nephrotoxicity of cephalosporins may also be increased in the presence of gentamicin. Consequently, monitoring of kidney function is advised if this combination is used.

Potent diuretics

If possible, do not give gentamicin in conjunction with etacrynic acid, furosemide or other potent diuretics which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Penicillins

Gentamicin is inactivated by solutions containing beta-lactam antibiotics (penicillins and cephalosporins) so the two drugs should not be administered simultaneously nor should they be combined in the intravenous fluid. This inactivation is brought about by the opening of the beta-lactam ring and combination of the penicillin with an amino group of gentamicin to form

a biologically inactive amide. For this reason, gentamicin and penicillins should not be combined in intravenous injections/infusions. The inactivation of gentamicin by penicillins may occur *in vivo*, especially in patients with renal failure who maintain a higher level of the penicillin for a longer period of time compared to patients with normal renal function. Therefore, when gentamicin and penicillins are used together in patients with renal failure, the time of administration of each drug should be staggered so that several hours separate each infusion.

Although the inactivation of gentamicin and penicillin proceeds on an equimolar basis, in practice the penicillin is present in such an excess that only the decline in activity of gentamicin is of concern. A combination of penicillin and gentamicin is often used in the treatment of enterococcal endocarditis.

Indometacin

Indometacin possibly increases plasma concentrations of gentamicin in neonates.

Neostigmine

Antagonism of effect may occur with concomitant administration of gentamicin with neostigmine.

Vitamin K

Gentamicin may inhibit the action of intravenous vitamin K upon the synthesis of clotting factors.

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

Australian Pregnancy Category D

Gentamicin and other aminoglycosides are known to cross the placenta. There is evidence of selective uptake of gentamicin by the fetal kidney resulting in cellular damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in-utero exposure to some of the aminoglycosides. Because of their chemical similarity, aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus.

Use in lactation

Aminoglycosides are excreted in breast milk in small but variable amounts. Although aminoglycosides are poorly absorbed from the gastrointestinal tract and problems in nursing infants have not been documented, it is not known whether they are harmful to the newborn. Therefore gentamicin should not be administered to lactating women unless the benefit clearly justifies the potential risks, including possible ototoxic and nephrotoxic effects on the baby.

4.7 Effects on ability to drive and use machines

The effect of gentamicin sulfate on the ability to drive or use machines has not been systematically evaluated. Patients should refrain from driving or using machines until they know that the medicinal product does not negatively affect these abilities.

4.8 Undesirable effects

These effects are reported in decreasing order of seriousness within each system organ class (SOC) and absolute frequency.

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000 to <1/100)**	**Rare (≥1/10 000 to <1/1 000)**	**Very rare (<1/10 000)**	**Frequency not known (cannot be estimated from the available data)**
Infections and infestations				Superinfection (with gentamicin-resistant bacteria), pseudomembranous colitis[*1]	Antibiotic associated colitis
Blood and lymphatic system effects		Dyscrasia		Thrombocytopenia, reticulocytopenia, leucopenia, eosinophilia, granulocytopenia, anaemia	
Immune system effects				Hypersensitivity reactions of varying severity, ranging from rash and itching, drug fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock	
Metabolism and nutrition effects			Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-		Tetany

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very rare (<1/10 000)	Frequency not known (cannot be estimated from the available data)
			Bartter syndrome in patients treated with high doses over a long period (more than 4 weeks), loss of appetite, weight loss		
Psychiatric effects				Confusion, hallucinations, mental depression	
Nervous system effects			Polyneuropathies, peripheral paraesthesias	Encephalopathy, convulsions, neuromuscular blockage, dizziness, balance disorder, headache*	Neurotoxicity[3]
Eye effects				Visual disorders	
Ear and labyrinth effects				Vestibular damage, hearing loss, Meniére's disease, tinnitus vertigo*	Irreversible hearing loss, deafness, ototoxicity, vestibular disorder
Vascular effects				Hypotension, hypertension	
Gastrointestinal effects			Vomiting, nausea, salivation increased, stomatitis, antibiotic-associated diarrhoea		
Hepatobiliary effects			Aspartate aminotransferase (AST)		Hepatic function abnormal

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very rare (<1/10 000)	Frequency not known (cannot be estimated from the available data)
			increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, serum bilirubin increased (all reversible)		
Skin and subcutaneous tissue effects		Allergic skin exanthema	Skin reddening	Toxic epidermal necrolysis[2], Stevens-Johnson syndrome[2], erythema multiforme[2], alopecia	
Musculoskeletal and connective tissue effects			Muscle pain (myalgia)	Amyostasia	
Renal and urinary effects	Renal function impairment[*]		Plasma urea increased (reversible)	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose[*]	Nephrotoxicity
Congenital, familial and genetic disorders					Fanconi syndrome acquired
General effects and administratio			Increased body temperature	Pain at injection site	

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to <1/100)	Rare (≥1/10 000 to <1/1 000)	Very rare (<1/10 000)	Frequency not known (cannot be estimated from the available data)
n site conditions					
Pulmonary effects	Respiratory depression, laryngeal oedema, pulmonary fibrosis				

* See also section 4.4 Special warnings and precautions for use.
1 Usually in these cases other antibiotics are also involved.
2 May occur as hypersensitivity reactions.
3 Including encephalopathy, confusion, lethargy, mental depression and hallucinations.

Nephrotoxicity

(see section 4.4)

Adverse renal effects, as demonstrated by the presence of casts, cells or protein in the urine or by rising BUN, NPN, serum creatinine or oliguria, have been reported. They occur more frequently in patients with a history of renal impairment and in patients treated for longer periods or with larger dosage than recommended.

Neurotoxicity

(see section 4.4)

Serious adverse effects on both vestibular and auditory branches of the eighth cranial nerves have been reported, primarily in patients with renal impairment (especially if dialysis is required), and in patients on high doses and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss, which, as with the other aminoglycosides, may be irreversible. Hearing loss is usually manifested initially by diminution of high-tone acuity. Other factors which may increase the risk of toxicity include excessive dosage, dehydration and previous exposure to other ototoxic drugs.

Peripheral neuropathy or encephalopathy, including numbness, skin tingling, muscle twitching, convulsions and a myasthenia gravis-like syndrome, have been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive DBL Gentamicin Injection BP at higher doses or for longer periods of time than recommended.

Other adverse reactions

Other reported adverse reactions possibly related to gentamicin include: respiratory depression, lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, and hypotension and hypertension; rash, itching, urticaria, generalised burning, laryngeal oedema, anaphylactoid reactions, fever, and headache, nausea, vomiting, increased salivation, and stomatitis; purpura, pseudotumor cerebri, acute organic brain syndrome, pulmonary fibrosis, alopecia, joint pain, transient hepatomegaly, and splenomegaly.

While local tolerance of DBL Gentamicin Injection BP is generally excellent, there has been an occasional report of pain at the injection site. Subcutaneous atrophy or fat necrosis suggesting local irritation has been reported rarely.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Peritoneal dialysis or haemodialysis will aid in the removal of gentamicin from the blood. This is particularly important in patients with renal malfunction.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Gentamicin is a bactericidal aminoglycoside antibiotic which acts by inhibiting protein synthesis of susceptible bacteria. It is effective against a wide variety of pathogenic aerobic gram negative bacilli and some gram positive organisms (see section 4.1). It is not active against anaerobic organisms.

5.2 Pharmacokinetic properties

Absorption

When gentamicin is administered intramuscularly, peak serum concentrations occur between 30 and 90 minutes after injection; effective concentrations persist for 6 to 8 hours.

Gentamicin is poorly absorbed by the oral route, and only minimal amounts have been found in the blood following oral administration.

In patients with normal renal function, peak serum concentrations of gentamicin, expressed in microgram/mL, are usually about four times the single dose expressed in mg/kg; for example, an injection of gentamicin 1 mg/kg may be expected to result in peak serum concentration of

approximately 4 microgram/mL. Gentamicin administered every 8 hours does not accumulate in the serum except in patients with impaired renal function in whom the serum concentration of gentamicin is usually higher, and measurable for longer periods. When gentamicin is administered by intravenous infusion, over 1 to 2 hours, the serum concentrations are similar to those obtained with intramuscular administration. About 25 to 30% of the administered dose of gentamicin is bound by serum protein; it is released as the drug is excreted. Gentamicin is excreted principally in the urine by glomerular filtration.

Distribution

Following parenteral administration, gentamicin can be detected in tissues and body fluids. Concentrations in bile in general have been low and have suggested minimal biliary excretion. Gentamicin administered intramuscularly has been found in low concentrations in the cerebrospinal fluid. Gentamicin has also been found in the sputum, pleural fluid, peritoneal, ascitic, pericardial, synovial and abscess fluids. Gentamicin crosses the peritoneal as well as the placental membranes.

Excretion

After initial administration to patients with normal renal function, 30 to 100% of the gentamicin is recoverable in the urine in 24 hours. High urine concentrations (above 100 microgram/mL) may be achieved. After several days treatment, the amount of gentamicin excreted in the urine approaches the daily dose administered. Renal clearance of gentamicin is similar to that of endogenous creatinine. The serum half-life of gentamicin is approximately 2-3 hours in adults with normal renal function. It is prolonged in patients with impaired renal function and in premature or newborn infants.

In patients with impaired renal function, the clearance of gentamicin is decreased; the more severe the impairment, the slower the clearance. Therefore, the interval between doses should be adjusted according to the degree of renal impairment. Endogenous creatinine clearance rate and serum creatinine, which have high correlation with serum half-life of gentamicin, may be used as a guide for this purpose (see section 4.2).

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ampoule product:

Disodium edetate dihydrate
Sulfuric acid
Sodium hydroxide
Water for injection

Ampoules of DBL Gentamicin Injection BP do not contain any antimicrobial preservative or antioxidant.

Vial product:

Disodium edetate dihydrate
Sodium methyl hydroxybenzoate
Sodium propyl hydroxybenzoate
Water for injection

Vials of DBL Gentamicin Injection BP contain sodium methyl hydroxybenzoate (2.06 mg/mL) and sodium propyl hydroxybenzoate (0.225 mg/mL) as preservative.

6.2 Incompatibilities

When gentamicin is used in combination with any other medicine mixing the medicines before administration should be avoided at all costs.

6.3 Shelf life

DBL Gentamicin 10 mg/mL Injection BP (glass ampoule): 36 months.

DBL Gentamicin 40 mg/mL Injection BP (glass ampoule): 36 months.

DBL Gentamicin 40 mg/mL Injection BP (glass vial and plastic ampoules): 24 months

*Note that not all presentations are marketed.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

DBL Gentamicin Injection BP 10 mg/mL gentamicin is supplied in 1 mL glass ampoules in packs of 5 ampoules.

DBL Gentamicin Injection BP 40 mg/ mL gentamicin is supplied in 2 mL glass vials or plastic ampoules or 2 mL glass vials in packs of 5 or 50 ampoules or vials.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited,

PO Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363
www.pfizermedicalinformation.co.nz.

9. DATE OF FIRST APPROVAL

DBLGentamicin 10 mg/mL Injection BP (TT50-3048b): 25 September 2008
DBLGentamicin 40 mg/mL Injection BP (TT50-3048): 14 January 1982

10. DATE OF REVISION OF THE TEXT

08 December 2022

Summary table of changes

All	Minor editorial changes throughout document.
2	Addition of information relating to sodium and sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate as excipients of known effects.
4.2	Relocation of the text relating to body weight within section 4.2 for better readability
4.4	Addition of warning of risk of allergic reaction from sodium methyl hydroxybenzoate and sodium propyl hydroxybenzoate as excipient of known effects
4.6	Removal of Pregnancy category footer note
6.1	Inclusion of excipients used for pH adjustment, relocation of preservative statement text to section 2.
6.3, 6.5 & 9	Removal of reference to DBL™ Gentamicin Injection BP Solution for injection, vials (presentation is not available)
8	Addition of Pfizer Medical Information contact details