

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Bleomycin Sulfate

15000 IU

Powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains bleomycin sulfate as a lyophilised powder, which is equivalent to 15,000 IU (15 units USP) bleomycin activity. Each vial contains 55-70% of bleomycin A₂ and 25-32% of bleomycin B₂.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DBL™ Bleomycin Sulfate for Injection is a white to cream coloured lyophilised powder or plug. When reconstituted in Water for Injection, the pH of the solution is approximately 5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Bleomycin Sulfate for Injection should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma: Head and neck including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingiva, epiglottis, skin, larynx, penis, cervix, and vulva. The response to bleomycin sulfate is poorer in patients with head and neck cancer previously irradiated.

Lymphomas: Hodgkin's disease and non-Hodgkin's lymphoma.

Testicular Carcinoma: Embryonal cell, choriocarcinoma, and teratocarcinoma.

DBL™ Bleomycin Sulfate for Injection is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusion. Single dose instillation is generally sufficient.

4.2 Dose and method of administration

Dose

Because of the possibility of anaphylactoid reaction, lymphoma patients should be treated with 2000 international units or less for the first 2 doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedules are recommended:

Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma: 250 to 500 international units/kg (10,000 to 20,000 international units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease: 250 to 500 international units/kg (10,000 to 20,000 international units/m²) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Pulmonary toxicity of bleomycin sulfate appears to be dose-related with a striking increase when the total dose is over 400,000 international units. Total doses over 400,000 international units should be given with great caution. *Note:* When bleomycin sulfate is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvements of Hodgkin's disease and testicular tumours is prompt and noted within two weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as three weeks before any improvement is noted.

Method of Administration

DBL™ Bleomycin Sulfate for Injection may be given by the intramuscular, intravenous, subcutaneous or intrapleural routes.

Intramuscular or Subcutaneous: Dissolve the contents of a DBL™ Bleomycin Sulfate for Injection vial in 1 to 5mL of Sterile Water for Injection, Sodium Chloride for Injection, or Bacteriostatic Water for Injection.

Intravenous: Dissolve the contents of the vial in 5mL or more of a solution suitable for injection, e.g. physiologic saline, and administer slowly over a period of ten minutes.

Malignant Pleural Effusion - 60,000 international units administered as a single dose bolus intrapleural injection.

For intrapleural administration dissolve 60,000 international units in 50-100 mL sodium chloride injection 0.9%, and administer through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The thoracostomy tube is then clamped. The patient should be moved from the supine to the left and right lateral position several times during the next four hours. The clamp is then removed and suction re-established.

The intrapleural injection of topical anaesthetics or systemic narcotic analgesia is generally not required.

As bleomycin is mostly excreted unchanged and as there is a high correlation between renal bleomycin clearance and creatinine clearance, modification of dose has been suggested for impairment of renal function. Dosage reductions of 40-75% have been recommended for patients with creatinine clearance values of ≤ 40 mL/min.

In order to minimize the incidence of pneumonitis due to bleomycin therapy, it is recommended not to exceed total dose 200,000 international units/m², not to exceed 100,000 international units/m² if concurrent lung irradiation is also given, not to exceed 100,000 international units/m² in patients over the age of 70, and to use continuous infusion to avoid peak serum levels.

4.3 Contraindications

DBL™ Bleomycin Sulfate for Injection is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

Patients with acute pulmonary infection or greatly reduced lung function.

A repeat course of therapy is contraindicated in any patient who has shown any signs of pneumonitis or decreased pulmonary function (see section 4.4).

4.4 Special warnings and precautions for use

It is recommended that Bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. Patients receiving bleomycin must be observed carefully and frequently during and after therapy.

After injection, bleomycin is readily absorbed and distributed in the body, particularly in the skin, lungs and any susceptible tumour tissue, leading to possible skin and pulmonary toxicity, as well as antitumour activity.

Gonadal suppression may occur and may be irreversible.

Cardiovascular

Bleomycin should be used with caution in patients with severe heart disease (see section 4.8).

Lymphoma patients

All lymphoma patients should receive test doses of bleomycin before initiating full-dose therapy (see section 4.8).

Pulmonary toxicity

No single predictive monitoring test for bleomycin-induced pulmonary toxicity has been identified. Frequent physical examinations should be undertaken. Cough, basal rales and pleuritic chest pain are frequent first signs of toxicity. Dyspnoea is usually the first symptom. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug-related. Pulmonary function tests [especially total lung volume

(TLV) and forced vital capacity (FVC)] may be of value in detecting early lung changes, although these are not always predictive of subsequent toxicity. It has been suggested that bleomycin should be discontinued if FVC decreases rapidly. Baseline and subsequent monthly evaluation of carbon monoxide diffusion capacity (DL_{CO}) are also recommended, and bleomycin should be discontinued when the DL_{CO} is less than 30-35% of the pre-treatment value.

The most commonly recommended method of monitoring the onset of pulmonary toxicity is weekly chest x-rays, which should be continued up to 4 weeks after completion of treatment. However, high resolution computer tomography is a more sensitive method of detection.

Other proposed methods of monitoring pulmonary toxicity include ^{99m}-Technetium scans and measurement of ESR, which has been found to increase prior to the development of symptomatic toxicity. However, the usefulness of these methods as predictors of development of toxicity have not been proven in clinical practice.

A method suggested to lower the incidence of pulmonary toxicity is the continuous intravenous administration of bleomycin.

- Anaesthesia

Because of bleomycin's effects on lung tissue, patients who have received the drug are at increased risk of developing pulmonary toxicity when oxygen is administered during surgery. Long exposure to very high concentrations of oxygen is a known cause of lung damage, but after administration of bleomycin, lung damage can occur at oxygen concentrations lower than those usually considered safe. Therefore to minimize the risk in patients undergoing surgery who have received bleomycin the following is recommended:

- i. FI O₂ concentration should be maintained at approximately that of room air (25%) during surgery and the post-operative period
- ii. Fluid replacement should be carefully monitored, with emphasis on administration of colloid rather than crystalloid.

- Pneumonitis

Pneumonitis due to bleomycin has been treated with corticosteroids in an effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

- Lung cancer

Bleomycin should be used with extreme caution in patients with lung cancer as these patients show an increased incidence of pulmonary toxicity.

- Compromised pulmonary function due to disease other than malignancy

Bleomycin should be used with extreme caution in patients with compromised pulmonary function as pulmonary toxicity may be particularly dangerous in these patients (see section 4.3).

- Previous cytotoxic or radiation therapy (especially chest irradiation); smokers

Bleomycin should be used with caution in patients who have had previous cytotoxic drug therapy or radiation therapy (especially chest irradiation), and in

patients who smoke, since the risk of pulmonary toxicity may be increased in these patients.

- **Cisplatin**
An increased incidence of bleomycin-induced pulmonary toxicity has been observed when these two agents are administered as part of an antineoplastic treatment regimen. Dosage reduction may be required (see section 4.5).
- **Granulocyte colony stimulating factor (G-CSF)**
It has been suggested that concomitant administration of G-CSF and bleomycin may increase the risk of bleomycin-induced pulmonary toxicity, especially at higher doses, although this has not been confirmed in clinical trials. If G-CSF is added to bleomycin-containing treatment regimens, patients should be closely observed for signs of pulmonary toxicity (see section 4.5).
- **Combination therapy**
Pulmonary toxicity may be observed at lower doses of bleomycin when bleomycin is administered as part of a multi-drug treatment regimen. Patients should be closely monitored for signs of pulmonary toxicity (see section 4.5).
- **Age related**
Patients over 70 years of age should be closely observed for signs of pulmonary toxicity due to bleomycin therapy (see section 4.8).
- **Cumulative dose**
Pulmonary toxicity is more common in patients receiving a total dose of more than 400,000 IU.

Renal or hepatic toxicity

Renal or hepatic toxicity, beginning as deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Cisplatin-induced renal function impairment may result in delayed clearance and bleomycin toxicity even at low doses (see section 4.5).

Use in renally impaired patients

Bleomycin should be used with extreme caution in patients with severely impaired renal function as clearance may be reduced and toxicity increased (see section 4.2)

Idiosyncratic reactions

Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of patients treated with Bleomycin (5% of lymphoma patients). Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

Effects on laboratory tests

No information available.

Other

The carcinogenic potential of bleomycin sulfate in humans is unknown. Given its mechanism of action, it should be considered to be a possible carcinogen in man. Bleomycin has been shown to be mutagenic in both *in vitro* and *in vivo* test systems. Bleomycin is teratogenic in rats and mice given the drug during organogenesis. The effects of bleomycin sulfate on fertility have not been established.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

- Anaesthetics, general, and oxygen

Use in patients previously treated with bleomycin may result in rapid pulmonary deterioration, since bleomycin causes sensitisation of lung tissue to oxygen.

- Radiation therapy

Radiation therapy, especially to the chest area, either prior to, during, or after bleomycin therapy may result in increased bleomycin toxicity. Dosage adjustment may be necessary.

- Antineoplastic agents

Concurrent use may result in increased bleomycin toxicity, or in occurrence of pulmonary toxicity at lower doses of bleomycin (see section 4.4).

- Combination therapy

Pulmonary toxicity may be observed at lower doses of bleomycin when bleomycin is administered as part of a multi-drug treatment regimen. Patients should be closely monitored for signs of pulmonary toxicity (see section 4.4).

- Granulocyte colony stimulating factor (G-CSF)

It has been suggested that concomitant administration of G-CSF and bleomycin may increase the risk of bleomycin-induced pulmonary toxicity, especially at higher doses, although this has not been confirmed in clinical trials. If G-CSF is added to bleomycin-containing treatment regimens, patients should be closely observed for signs of pulmonary toxicity (see section 4.4).

Pharmacokinetic interactions

- Cisplatin

Cisplatin-induced renal function impairment may result in delayed clearance and bleomycin toxicity even at low doses. An increased incidence of bleomycin-induced pulmonary toxicity has been observed when these two agents are administered as part of an antineoplastic treatment regimen. Dosage reduction may be required (see section 4.4).

- Digoxin

Serum levels of Digoxin may be reduced and its actions may be decreased. It is thought that drug-induced alterations of the intestinal mucosa may be involved in the reduced GI absorption.

- Phenytoin

Serum concentrations of phenytoin may be decreased due to decreased absorption or increased metabolism of Phenytoin.

4.6 Fertility, pregnancy and lactation

Fertility

The effects of bleomycin on fertility are not known.

Pregnancy

Category D. Bleomycin has caused, is suspected to have caused or may be expected to cause, an increase incidence of human foetal malformations or irreversible damage. It may also have adverse pharmacological effects.

Lactation

It is not known whether bleomycin is excreted in breast milk. Due to the potential for serious adverse effects in infants, it is recommended that breastfeeding is discontinued prior to administration of bleomycin sulfate to the mother.

4.7 Effects on ability to drive and use machines

Bleomycin Sulfate may be likely to produce minor or moderate adverse effects that may impair the patient's ability to concentrate and react and therefore constitute a risk in the ability to drive and use machines.

4.8 Undesirable effects

Serious or Life Threatening Effects

Pulmonary toxicity

The most serious toxicity of Bleomycin is a subacute or chronic pneumonitis that progresses to interstitial fibrosis and may be fatal. This occurs in approximately 10% of treated patients, about 1% of whom have died of pulmonary fibrosis. Pulmonary toxicity is both age and dose related, being more common in patients over 70 years of age and in those receiving over 400,000 IU total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Also, when used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

This toxicity is frequently seen in those with underlying lung disease such as emphysema and in those previously treated with pulmonary or mediastinal irradiation.

The identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult. The clinical symptoms and x-ray findings of bleomycin pulmonary toxicity are not easily distinguished from other syndromes commonly observed in cancer patients, including progressive metastatic tumour (especially lymphangitic tumour), infectious processes such as *Pneumocystis carinii* or cyto-megalovirus, or radiation injury.

The first symptoms to appear are dyspnoea, with cough, fine rales and low grade fever, commonly occurring 4-10 weeks after initiation of therapy, although the time of onset of pulmonary toxicity may vary from during therapy to up to six months after the cessation of therapy.

The microscopic tissue changes due to bleomycin toxicity are frequently present as bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous oedema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome.

These microscopic findings are non-specific and are similar to the changes produced in radiation pneumonitis, pneumocystic pneumonitis, and at times reaction to long standing malignant pulmonary disease.

Pulmonary function tests have revealed some alteration in the pulmonary status such as decreased total lung volume and decreased vital capacity, but these tests have proved to be of limited value in predicting pulmonary fibrosis. It has been suggested that Bleomycin should be discontinued if forced vital capacity decreases rapidly.

Pulmonary toxicity is seen more commonly in smokers. **Idiosyncratic Effects**

Hypersensitivity reactions consisting of hypotension, fever, chills, mental confusion and wheezing have occurred in approximately 1% of patients receiving bleomycin.

This idiosyncratic reaction occurs mainly in lymphoma patients (5%), may be immediate or delayed for several hours, and usually occurs after the first or second dose. The reaction has resulted in death. Treatment of anaphylactoid reactions is supportive and symptomatic and may include volume expansion, vasopressor therapy, antihistamines, and corticosteroids.

Cardiovascular

Vascular toxicities coincident with the use of bleomycin in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (haemolytic – uremic syndrome) or cerebrovascular arteritis. Acute chest pain syndrome, acute pericarditis, fulminant fatal hyperpyrexia and fulminant, fatal angioedema have been reported.

More Common Effects

Body as a whole: Fever, chills and headache frequently follow parenteral administration of bleomycin (20-50%). These reactions have been reported to occur most frequently with large single doses and occur within a few hours of administration lasting 4-12 hours. Usually,

febrile reactions become less frequent with continued use of the drug but may occur sporadically and re occur later in the treatment course.

Gastrointestinal: Anorexia, mucositis, nausea and vomiting (20-50%) (anorexia and weight loss may persist after discontinuing therapy), tiredness.

Mucocutaneous (50%): Hypoesthesia which may progress to hyperesthesia, urticaria, erythematous swelling, tenderness, pruritis, hyperpigmentation (particularly in those areas subject to friction or pressure and in skin folds, nail cuticles, scars, and I.M. injection sites), patchy hyperkeratosis, alopecia, ichthyosis, rash, striae, vesiculation, peeling, and bleeding, stomatitis, ulcerations of the tongue and lips. This toxicity is usually evident within 2nd or 3rd week following initiation of therapy and appears to be reversible and dose related, usually after 150,000 to 200,000 IU of bleomycin has been administered and, in general, is related to total cumulative dose. In 2% of patients it was necessary to discontinue treatment because of this toxicity.

When bleomycin is administered intra-arterially, dermal lesions are most common in the region supplied by the artery used. The incidence of mucocutaneous adverse events is increased when bleomycin sulfate is given in combination with radiotherapy to head and neck.

Less Common Effects

Body as a whole: Idiosyncratic reactions occurring in 1% of patients (5% of lymphoma patients) (see above).

Cardiovascular: Diverse vascular toxicities (see above), hypotension (more common after intra-pleural administration), sudden onset of an acute chest pain syndrome, suggestive of pleuropericarditis (although each patient must be individually evaluated, further courses of bleomycin do not appear to be contraindicated), ocular haemorrhage.

There are isolated reports of Raynaud's phenomenon occurring in patients treated with a combination of bleomycin and vinblastine with or without cisplatin, or, in a few cases, with bleomycin as a single agent. It is currently unknown if the cause of the Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, cisplatin-induced hypomagnesaemia or a combination of any or all of these.

Central Nervous System: CNS toxicity is rare, but monitoring is advised. Disorientation and aggressive behaviour have been reported.

Haematologic: Thrombocytopenia, leukopenia, slight depression of haemoglobin levels. Bleomycin does not frequently produce serious bone marrow toxicity.

Hepatic: Liver toxicity beginning as deterioration in liver function tests has been reported infrequently.

Injection site: Pain at injection site, phlebitis, other local reactions.

Renal: Renal toxicity beginning as deterioration in renal function tests has been reported infrequently.

Haematuria and cystitis have been reported.

Respiratory: Pulmonary toxicity (10%) (see above).

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

Symptoms

There has been no reported case of overdosage. The acute reaction would probably include hypotension, fever, rapid pulse and general symptoms of shock.

Treatment

There is no specific antidote for Bleomycin overdosage. Treatment should be symptomatic and supportive. In the event of respiratory complications treatment with a corticosteroid may be beneficial and the administration of a broad spectrum antibiotic is advisable. Bleomycin is probably not dialysable.

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

Bleomycin sulfate is an antineoplastic antibiotic which is a purified mixture of glycopeptides produced by a fermentation process employing the actinomycetes *Streptovercillium* species. The bleomycin mixture contains predominantly the A₂ and B₂ peptides.

Mechanism of action

Bleomycin sulphate is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

Although the exact mechanism of action of bleomycin is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

When administered intrapleurally for the treatment of malignant pleural effusion, bleomycin acts as a sclerosing agent. Following intrapleural administration the resultant bleomycin plasma concentrations suggest a systemic absorption rate of approximately 45%.

5.2 Pharmacokinetic properties

In mice, high concentrations of bleomycin are found in the skin, lungs, kidneys, peritoneum and lymphatics. Tumour cells of the skin and lungs have been found to have high concentrations of bleomycin in contrast to the low concentrations found in haematopoietic tissue. The low concentrations of bleomycin found in bone marrow may be related to high levels of bleomycin degradative enzymes found in that tissue.

In patients with a creatinine clearance of > 35mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of < 35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. In humans, 60 to 70% of an administered dose is recovered in the urine as active bleomycin. Protein binding of bleomycin is less than 1%.

An association between decreased renal function and enhanced bleomycin-related toxicities has been reported. Pharmacokinetic/pharmacodynamic relationships suggest that enhancement of toxicity is a consequence of reduced renal clearance of bleomycin resulting in prolonged elimination half-life and increased area-under-the-plasma-concentration-vs.-time-curve compared to patients with normal renal function. Dosage reductions of 40-75% have been recommended for patients with creatinine clearance values \leq 40 mL/min.

5.3 Preclinical safety data

Genotoxicity

Bleomycin is mutagenic in both *in vitro* and *in vivo* test systems.

Mutagenicity

It is not known whether bleomycin is carcinogenic in humans. However, an increased incidence of nodular hyperplasia was noted in F344/N male rats with lung cancer induced by nitrosamines, after bleomycin treatment. In another study where bleomycin was administered subcutaneously to rats at a dose of 0.35mg/kg weekly (or about 30% the recommended human dose), necropsy findings included dose related injection site fibrosarcomas and various renal tumours.

Reproductive and developmental toxicity

The effects of bleomycin on fertility are not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection

6.2 Incompatibilities

No data available.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

DBL™ Bleomycin Sulfate for Injection is available in vials containing 15,000 IU (15 units USP) of bleomycin.

Pack size: 1 or 10 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Directions for reconstitution

For intramuscular or subcutaneous injection: dissolve the contents of the vial in 1-5mL of Sterile Water for Injection or Sodium Chloride Intravenous Infusion 0.9%.

For intravenous or intra arterial injection: dissolve the contents of the vial in 5-10mL of diluent and administer slowly over a period of 10 minutes.

Suitable diluents are Water for Injections, Bacteriostatic Water for Injection and Sodium Chloride Intravenous Infusion 0.9%. Although Glucose Intravenous Infusion 5% has been used in the past, recent data suggests that it is not the diluent of choice, as over the concentration range of 300 to 15,000 IU (0.3 - 15units USP) /mL the content of Bleomycin A₂ + B₂ was consistently lower when Glucose Intravenous Infusion 5% was used.

Reconstituted solutions containing 150 to 15,000 IU (0.15 - 15units USP)/mL bleomycin prepared using the recommended diluents remain stable for periods of at least 24 hours when stored in the dark, at temperatures of 2-8°C or 25°C. Solutions of bleomycin sulfate in Sodium Chloride Intravenous 0.9% stored in the dark at 2-8°C for 10 days were chemically stable. However, in order to reduce the possibility of microbiological contamination, reconstituted injections should be used as soon as practicable after preparation. If storage of the reconstituted solution is necessary, store at 2-8° C for no more than 24 hours.

Any unused medicine or waste material should be disposed of in accordance with local requirements for the disposal of anticancer drugs.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

23 September 1993

10. DATE OF REVISION OF THE TEXT

21 October 2020

Summary table of changes

Section changed	Summary of new information
4.2	Safety information updated to clarify method of administration information
4.4	Safety information updated to include additional precautions
4.8	Additional Adverse events added