MINOR VARIATION NOTIFICATION FORM FOR FULL EVALUATION PRODUCTS

Please read the following instructions before filling in the form.

1) This notification form is for Product Registration Holder (PRH) to notify National Pharmaceutical Control Bureau (NPCB) on the implementation of MiV-Notification (MiV-N) as per Malaysian Variation Guideline (MVG). The timeline for NPCB to acknowledge the variation notification is within 20 working days following receipt of a notification.
2) Please refer to the MVG for the conditions and supporting documents required.
3) Submission of relevant revised draft of package insert and labeling is subject to current regulatory requirements as per the latest Drug Registration Guidance Document (DRGD) and Circulars from NPCB. In the event that the revised draft of package insert and labeling does not meet the current regulatory requirements, please submit under Minor Variation Prior Approval (MiV-PA) or Major Variation (MaV).
4) PRH must submit this notification form together with the online submission through the Quest 2 system as the approval will only be notified via online submission. For submission online, please scan this form and attach together with the revised draft of package insert and labeling as a single file.
5) A MiV-N application may be rejected in specific circumstances with the consequence that the PRH must cease to apply the already implemented variation.
6) The completed form must be submitted to :
   Seksyen Variasi, Pusat Pasca Pendaftaran Produk, Biro Pengawalan Farmaseutikal Kebangsaan, Kementerian Kesihatan Malaysia, Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor. (Fax No: 03-79567151)

Product Name: **A.D. MYCIN INJECTION 2MG/ML**	Name and address of product registration holder: FIRST PHARMACEUTICAL SDN. BHD 20, Jalan SS 19/5, 47500 Subang Jaya, Selangor
Reference Number:	Tel. No.: 03-56340669
Registration Number: MAL06061702A	Fax No.: 03-56340990
Date of online submission in Quest System: 25 July 2013	Email address: khmsb@streamyx.com

Variation No.	Minor Variation (Notification)	Please tick (√) *Multiple selection is allowed*
MiV-N1	Change of details of product registration holder	
MiV-N2	Change of importer and/or store address	
MiV-N3	Change of product owner	
MiV-N4	Change in ownership of manufacturer	
MiV-N5	Change of the name or address (for example: postal code, street name) of the manufacturer of drug product	√
MiV-N6	Change of the name or address (for example: postal code, street name) of the company or manufacturer responsible for batch release	
MiV-N7	Change of the name and/or address (for example: postal code, street name) of a manufacturer of the drug substance	
MiV-N8	Withdrawal/deletion of the alternative manufacturer(s) for drug substance	
MiV-N9	Renewal of European Pharmacopoeial Certificate of Suitability (CEP)	
MiV-N10	Change of specifications of the drug product and/or drug substance and/or excipient, following the updates in the compendium	
MiV-N11	Deletion of pack size for a product	

I hereby notify NPCB on the minor variation by notification for the product(s) above and declare that

- ✓ There is no other change except for the proposed variation;
- ✓ The change(s) will not adversely affect the quality, efficacy and safety of the product;
- ✓ All conditions for the variation concerned are fulfilled;
- ✓ The required supporting documents as specified for the variation in MVG have been submitted; and
- ✓ The proposed change has been checked in reference with the currently approved data in the system & there are no discrepancies.

Lim Chin Leong		25 July 2013
Name	Signature	Date

120*300

A.D.mycin® Injection
(Doxorubicin • HCl) 2mg/mL

Name and Strength of Active Ingredient

DOXORUBICIN HYDROCHLORIDE 2mg/mL

Product Description Clear and red solution

Pharmacodynamics

Doxorubicin hydrochloride is an antineoplastic antibiotic with pharmacologic actions similar to those of Daunorubicin. Although the drug has anti-infective properties, its cytotoxicity precludes its uses as an anti-infective agent. the precise and/or principal mechanisms of the antineoplastic action of doxorubicin is not fully understood. It appears that the cytotoxic effect of the drug results from a complex system of multiple modes of action related to free radical formation secondary to metabolic activation of the doxorubicin by electron reduction, intercalation of the drug into DNA, induction of DNA breaks and chromosomal aberrations, and alterations in cell membranes induced by the drug. Evidence from in vitro studies in cells treated with doxorubicin suggests that apoptosis (programmed cell death) also may be involved in the drug's mechanism of action. These and other mechanisms (chelation of metal ions to produce drug-metal complexes) also may contribute to the cardiotoxic effects of the drug.

Doxorubicin undergoes enzymatic 1- and 2- electron reduction to the corresponding semiquinone and dihydroquinone. 7-Deoxyaglycones are formed enzymatically by 1-electorn reduction, and the resulting semiquinone free radical reacts with oxygen to produce the hydroxyl radical in a cascade of reactions; this radical may lead to cell death by reacting with DNA, RNA, cell membranes, and proteins. The dihydroquinone that results from 2-electron reduction of doxorubicin also can be formed by the reaction of 2 semiquinones. In the presence of oxygen, dihydroquinone reacts to form hydrogen proxide, and in its absence, loses its sugar and gives rise to the quinone methide, a monofuctional alkylating agent with low affinity for DNA. The contribution of dihydroquinone and the quinone methide to the cytotoxicity of doxorubicin is unclear. Experimental evidence indicates that doxorubicin forms a complex with DNA by intercalation between base pairs, causing inhibition of DNA synthesis and DNA0dependent RNA synthesis by the resulting template disordering and steric obstruction. Doxorubicin also inhibits protein synthesis. Doxorubicin is active throughout the cell cycle including the interphase.

Of the cell types tested in vitro, cardiac cells are the most sensitive to the effects of doxorubicin, followed by sarcoma and melanoma cells, normal muscle fibroblasts, and normal skin fibroblasts. Normal, rapidly proliferating tissues such as those of bone marrow, GI and oral mucosa, and hair follicles are also affected to varying degrees. Doxorubicin hydrochloride also has immunosuppressive activity.

Pharmacokinetics

Distribution:

An intravenous bolus injection of doxorubicin produces high plasma concentrations, which fall quickly due to rapid and extensive distribution into tissues. 50 to 85% of plasma doxorubicin in bound to protein, independent of the absolute drug concentration in plasma, leaving 15 to 50% of the total doxorubicin and doxorubicinol as free drug. After repeated injections no accumulation in plasma occurs. Apparent volumes of distribution are in the range of 20 to 30L/kg.

Doxorubicin dose not cross the blood-brain barrier and is therefore inactive against tumours in the central nervous system. Some transplacental passage has been observed, although healthy children have been born after pregnancies during which doxorubicin was administered from the first to the third trimester. Negligible doxorubicin concentrations have been found in breast milk. Salivary doxorubicin concentrations are 6 to 26% of plasma concentrations during the first 75 minutes after administration.

Metabolism:

Doxorubicin is rapidly metabolized into the hydrophilic 13-hydoxyl metabolite, doxorubicinol, and the poorly water-soluble aglycones, doxorubicinone and 7-deoxydoxorubicinone. Metabolism to doxoruicinol occurs by cytoplasmatic NADPH-dependent aldoketoreductases, present in all cells, but particularly in red cells, and liver and kidney cells. The non-cytotoxic aglycones are formed by and NADPH-dependent, cytochrome reductase-mediated clearage of the amino sugar moiety in microsomes. This enzymatic reduction of doxorubicin is paramount importance, as it finally produces the OH-radicals, which cause extensive cell damage and cell death.

Elimination:

Doxorubicin and its catabolites are primarily excreted in the bile. Over 50% is eliminated during the first transit through the liver. Cumulative faecal excretion over 7 days has been estimated at 25 to 45%; no evidence for enterohepatic recirculation has been observed. Although patients often notice a reddish colouration of the urine during the first hours o days after doxorubicin administration, only 0.7 to 23%(on average, approximately 5%) of a dose has been recovered in the urine, of which approximately two-thirds is unaltered drug. Nevertheless, doxorubicin-induced nephrooxicity has been noted only in mice, rats, rabbits and dogs, and not in humans. The reason for this interspecies difference has not been explained, although stimulated lipid peroxidation may play a role.

Large inter- and intra-patient variations in doxorubicin pharmacokinetics may be related to some extent to individual differences in metabolism, toxicity and efficacy. On the other hand, an attempt to correlate plasma pharmacokinetic parameters with clinical parameters has failed. The pharmacokinetics of doxorubicin are linear. The doxorubicin plasma concentration-time curve can be best described by a biexponential model, which is characterized by a distribution half-life of less than 5 to 10 minutes, and a terminal phase elimination half-life of 30 +/-8 hours. A triphasic curve with half-lives of 12+/-8 minutes, 3.3 +/- 2.2 hours and 30 +/- 14hours has also been proposed.

Dose-dependent and age-dependent early-phase pharmacokinetics have been assumed, but these were not confirmed in later studies. In addition, time-, species- and tumour burden-dependent variations in pharmacokinetics have been reported. In children, different pharmacokinetics have been reported, i.e. greater clearance than observed in adults.

The intrinsic half-life of doxorubicinol in dogs was 3.7 hours, whereas after administration of doxorubicin the half-life of both doxorubicin and doxorubicinol was 30 hours. The ratio of the doxorubicinol: doxorubicin area under the plasma concentration-time was 0.4 to 0.9. small amounts of aglycones have been detected in a minority of patients, but the clinical significance of these metabolites in unclear.

Indication

Doxorubicin has been used successfully to produce regression in neoplastic conditions such as acute leukaemia, Wilms' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, lymphomas of both Hodgkin's and non-Hodgkin's type, bronchogenic (lung) carcinoma, thyroid carcinoma, hepatomas, ovarian carcinoma, etc.

Doxorubicin is also indicated by intravesical administration in the primary management of non-metastatic carcinoma of the bladder (Tis,T1, T2)

Doxorubicin has some antitumor activities against stomach, cervix, head and neck, testicle, myeloma and endometrial cancer.

Recommended Dose

Care in the administration of Doxorubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. The recommended dosage schedule is 60-75mg/m^2 as a single intravenous injection administered at 21 day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 30mg/m^2 on each of three successive days repeated every 4 weeks. The adult dosage regimens may be suitable for pediatric cases. The recommended lifetime cumulative dose limit is 550mg Doxorubicin body surface area. Doxorubicin has been administered as an intra-arterial Infusion for 1-3 days at doses of 45-100mg/m^2. It is recommended that the total cumulative dose of Doxorubicin for adults aged 70 or older be restricted to 450mg/m^2 body surface area. Doxorubicin dosage must be reduced if hepatic function is impaired according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
1.2 – 3.0 mg/100ml	9 - 15%	50% Normal dose
> 3.0 mg/100ml	>15%	25% Normal Dose

Doxorubicin Injection must be handled with care. If contact with the skin occurs, wash thoroughly with soap and water. The product does not contain a preservative. The solution is to be stored under refrigeration (2-8°C) and should be protected from sunlight and retained in the carton until time of use. It is recommended that Doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection USP or 5% Dextrose Injection US. The tubing should be attached to a butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However the dose should be administered in not less than 3-5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous. Infiltration and the infusion should be immediately terminated and restarted in another vein. Doxorubicin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that Doxorubicin be mixed with other drugs. Doxorubicin has been used in combination with other approved chemotherapeutic agents. Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents the benefits and risks of such therapy have not yet been fully elucidated. Intravesical Administration The following procedure is recommended: The bladder should be catheterized and emptied. Dissolve 80mg of Doxorubicin in 100mL of normal saline and instill via the catheter into the bladder. The catheter should be removed and the patient instructed to be on one side. At 5 minute intervals the patient should alternate to the opposite side over a 1 hour period. The patient should be requested not to urinate for 1 hour, after which the bladder should be emptied of solution. The procedure should be repeated at monthly intervals.

Route of Administration Intravenous infusion

Contraindication

1) Patients with impaired heart function or pre-existing heart disease.
2) Patients with severe hypersensitivity to this drug.
3) Patients with myelosuppression induced by prior treatment with other antitumor agents or by radiotherapy.
4) Patients with previous treatment with doxorubicin, Daunorubicin, idarubicin or/ and anthracyclines and antracene up to the maximum cumulative dose.
5) Pregnant women and nursing mother.
6) Patients with administered yellow fever vaccine or phenytoin as preventive.

Warning and Precautions

1. Special attention must be given to following patients
   1) Patients with impaired hepatic function
   2) Patients with impaired renal function (adverse reaction could be increased)
   3) Patients with infection symptoms
   4) Patients with myelosuppression (adverse reaction could be increased)
   5) Very old patients
   6) Patients with hydrocephalus (fatal systemic disorder may occur.)
   7) Patients with radiotherapy or plan to radiotherapy
   8) Patients with diarrhea
2. General cautions
   1) Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agent in fully qualified institute.
   2) This drug is very toxic. Therefore both powder and solution should be treated with cause. If inhale powder or evaporation or contact with skin and mucosa such as eye, in case of eyes, prompt wash with copious amounts of water and proceed to a physician for medical evaluation and in case of skin contact, flush with copious amounts of water for at least 15 minutes.
   3) Since severe adverse reactions such as bone marrow suppression and cardiomyopathy may occur, appropriate clinical test(blood test, hepatic function test, renal function test and heart function test) should be performed and fully observation is required .When abnormal signs do occur, proper treatment such as reducing the quantity and discontinuation should be taken. Also since severe and continuous adverse reactions may occur due to long term therapy, administration should be careful.
   4) Be careful infectious and bleeding complications may occur
   5) Doxorubicin may effect sexual gland when administered to children or patients of childbearing potential.

Pediatric use

Since safety for immature infant, newborn, infant and child has not been established, extremely be careful to manifest side effects.

Caution in use

1) It is recommended to avoid intramuscular injection or hypodermic injection.
2) Because intraperitoneal injection may cause intestinal accretion, it should be avoided.
3) On intravenous administration pain on blood vessel, phlebitis and thrombus may occur, so be careful about the site of injection and how to inject and inject as slow as possible.
4) Since on intravenous injection extravasation cause induration and necrosis on the injection site, be careful to avoid extravasation
5) As reconstitution, stability could be decreased by pH, therefore it is not recommended to inject after mixing with other drugs, administer after reconstitute with water for injection or normal saline.
6) Use quickly after reconstitution.
7) Doxorubicin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form.

Others

1) Red coloration of urine is reported.
2) Breast tumor has been reported in rats with intravenous injection.
3) Acute leukemia and myelodysplastic syndrome(MDS) have been reported in patients with combination therapy of other antineoplastics

Interactions With Other Medicaments

High dose cyclosporin increases the serum levels and myelotoxicity of doxorubicin.

Pregnancy and Lactation

There is no conclusive evidence as to whether doxorubicin may adversely affect human fertility or cause teratogenesis. Experimental data however suggest that doxorubicin may harm the fetus and should not therefore be administered to pregnant women or those who are breast feeding.

Side Effects

Hematological monitoring should be undertaken regularly in both hematological and non hematological conditions, because of the possibility of bone-marrow depression which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/hematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, hemorrhages, tissue hypoxia or death.
The occurrence of secondary acute myeloid leukemia with or without a pre-leukemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA damaging anti-neoplastic agents. Such cases could have a short (1-3 year) latency period.
Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly, without premonitory ECG changes.
Doxorubicin solution for injection may impart a red color to the urine particularly to the first specimen passed after the injection, and patients should be advised that there is no cause for alarm.
Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally returns after treatment is stopped. Nausea, vomiting and diarrhea may also occur.
The risk of thrombophlebitis at the injection site may be minimized by following the procedure for administration recommended above. A stinging or burning sensation signifies a small degree of extravasation and the infusion should be stopped and restarted in another vein.
Other side effects include mucositis, skin rashes, fever, hyperuricemia, amenorrhea, anaphylaxis, bronchospasm and dyspnea.

Symptoms And Treatment of Overdose

1) Symptoms: Acute myocardial degeneration, angina, severe heart failure including myocardial infarction, granulocytopenia, severe myelosuppression such as thrombocytopenia 10 days after administration, severe mucositis and bowel necrosis, and hepatotoxicity may occur. Also in case that total dose is more than 550mg/m^2, the risk of cardiomyopathy and congestive heart failure is increased.
2) Treatment: Since this medicine is excreted through bile and the intestinal tract carry out with transfusion, antimicrobials, platelet transfusion and myelosuppressive treatment instead of hemodialysis and use of hemopoietic growth factor (G-CSF, GM-CSF) may be considered. Cardiant, diuretic and ACE inhibitor should use for treatment congestive heart failure.

Storage Condition

Store at 2 – 8 degree Celsius, protected from light

Pack Size

10mg/5ml per vial; 50mg/25ml per vial

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Manufactured by
BORYUNG pharm
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