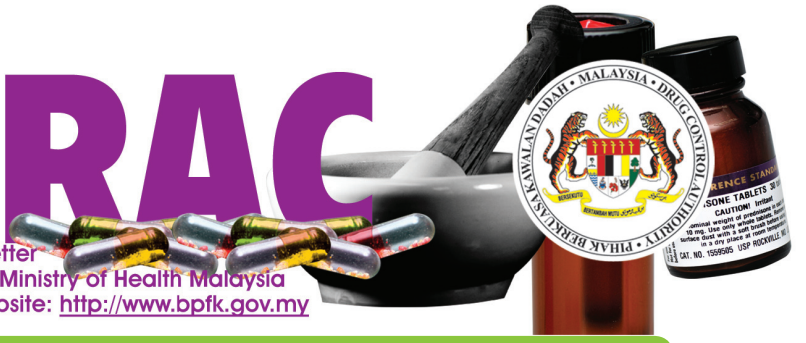
AUGUST 2011

MADRAC

Malaysian Adverse Drug Reactions Newsletter
National Pharmaceutical Control Bureau, Ministry of Health Malaysia
This newsletter is also available on our website: http://www.bpfk.gov.my



REGULATORY MATTERS

5-ALPHA REDUCTASE INHIBITORS: INCREASED RISK OF HIGH GRADE PROSTATE CANCER

The 5-alpha reductase inhibitor (5-ARI) class of drugs has been found to be associated with an **increased risk of a more serious form of prostate cancer** (high-grade prostate cancer). This risk appears to be low, but healthcare professionals are advised to weigh the known benefits against the potential risks when deciding to start or continue treatment with 5-ARIs in men.

Drugs in the 5-ARI class include **finasteride** and **dutasteride**. In Malaysia, finasteride 5mg and dutasteride are indicated for the treatment and control of symptomatic **benign prostatic hyperplasia** (BPH), as well as to reduce the risk of acute urinary retention or the need for BPH-related surgery. Finasteride 1mg, on the other hand, is indicated for the treatment of **male pattern hair loss** (androgenetic alopecia).

Data summary

This new safety information is based on the review of two large randomised control trials, namely PCPT and REDUCE trial.

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CONTENT

To report an adverse drug reaction:

1. Visit http://www.bpfk.gov.my;
2. Click on "MADRAC (Adverse Drug Reactions)" on the left toolbar; and
3. Click on "Reporting Online".

Alternatively, please contact:

National Centre for Adverse Drug Reactions Monitoring
Centre for Post Registration of Products
National Pharmaceutical Control Bureau
Ministry of Health
Peti Surat 319, Jalan Sultan,
46730 Petaling Jaya,
Selangor.

Tel : +603-7883 5400
Fax : +603-7956 7151

	PCPT	REDUCE
Reference	Thompson IM, Goodman PJ, Tangen CM, et al. The Influence of Finasteride on the Development of Prostate Cancer. N Engl J Med. 17 July 2003; 49(3): 215-224.	Andriole GL, Bostwick DG, Brawley OW, et al. Effect of Dutasteride on the Risk of Prostate Cancer. N Engl J Med. 1 April 2010; 362(13): 1192-1202.
Study Design	• Multicentre, randomised, double-blind, placebo-controlled • 18,882 men aged 55 years or older	• Multicentre, randomised, double-blind, placebo-controlled • 8,231 men aged 50-75 years
Objective	To compare the use of finasteride 5mg to placebo for the reduction in the risk of prostate cancer.	To evaluate the efficacy and safety of once daily dosing of dutasteride in reducing the risk of biopsy-detectable prostate cancer.
Intervention	• finasteride 5mg (n=9423), placebo (n=9459) • continued for 7 years	• dutasteride 0.5mg (n=4105), placebo (n=4126) • continued for 4 years
Results	Similar results were observed in both studies: • Treatment arm had an overall lower risk of being diagnosed with prostate cancer when compared to placebo arm. [**PCPT** finasteride arm 26% lower, **REDUCE** dutasteride arm 23% lower; both p<0.0001] • Risk reduction was limited to Gleason score (GS) 6 or lower prostate cancers. • There was an increased incidence of GS 8-10 prostate cancers with treatment vs placebo. [**PCPT** finasteride 1.8% vs placebo 1.1%, **REDUCE** dutasteride 1% vs placebo 0.5%]	

Local Scenario

There are seven 5-ARI products registered in Malaysia, of which six contain finasteride (5mg: Finaintas, Finast, Fincar, Proscar; 1mg: Finapecia, Propecia) and the remaining one dutasteride (Avodart).

In 2010, package inserts for all products containing finasteride 5mg and dutasteride had been updated to include the recommendation to conduct **digital rectal examinations** as well as other evaluations for prostate cancer prior to initiation of 5-ARI therapy, and periodically thereafter. Information regarding the **effects of 5-ARI on prostate-specific antigen (PSA) and prostate cancer detection** was also added.

The National Centre of ADR Monitoring has received 39 reports related to finasteride (2000 to June 2011) and 10 reports related to dutasteride (2007 to June 2011). No report on prostate cancer has been received.

Regulatory Action

In July 2011, MADRAC had proposed to update the package insert of all 5-ARI products with this new safety information. The proposal was accepted by DCA in its 242nd meeting on 28 July 2011. New information that is to be added is as follows:

WARNINGS & PRECAUTIONS

Finasteride	***Increased Risk of High-Grade Prostate Cancer*** *Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo).* *5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.*
Dutasteride	***Increased Risk of High-Grade Prostate Cancer*** *In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).* *5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study related factors, impacted the results of these studies has not been established.*

Reference:

1. FDA MedWatch.FDA Drug Safety Communication: 5-alpha reductase inhibitors (5-ARIs) may increase the risk of a more serious form of prostate cancer.
http://www.fda.gov/Drugs/DrugSafety/ucm258314.htm [9 June 2011]

BETA AGONISTS: STRENGTHENED WARNINGS AGAINST USE IN PRETERM LABOUR

Using terbutaline in the treatment of preterm labour may pose risk of **serious heart problems and death** in pregnant mothers. This announcement from the US Food and Drug Administration (US FDA) was made following the review of post-marketing safety reports of terbutaline used for obstetrical indications and data from medical literature.

The associated serious adverse events include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia.

Other than for the treatment of respiratory diseases, beta agonists are also used **off-label** (internationally and locally) for acute obstetric uses, including treating preterm labour and uterine hyperstimulation.

Data suggested that:

- **injectable** terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labour in either hospital or outpatient setting;

- **oral** terbutaline should not be used for prevention or any treatment of preterm labour because it has not been shown to be effective and has similar safety concerns.

However, it may be deemed appropriate based on the healthcare professional's judgement to administer terbutaline by injection in urgent and individual obstetrical situations in the hospital setting.

This safety update is **not applicable** to syrups, suspensions and inhalation products as such dosage forms are not used for the aforementioned purpose.

Local Scenario

On 11 November 2010, *Mesyuarat Panel Kajisemula Senarai Ubat KKM* had approved the off-label use of certain tocolytic agents, including terbutaline 0.5mg/ml injection, salbutamol 5mg/5ml injection, terbutaline 2.5mg tablet and salbutamol 2mg tablet, in preterm labour. Dosing guidelines for the off-label use of these drugs have been prepared and distributed to all Ministry of Health facilities.

There are 1 injectable and 3 oral (tablet and capsule) terbutaline, as well as 3 injectables and 12 oral (tablet and capsule) salbutamol products registered with the DCA.

As of August 2011, the National Centre of ADR Monitoring has received 1 report on **injectable** terbutaline for the indication of tocolysis. Itching, rash, tachycardia and tremor happened a few hours after treatment. The patient recovered without sequelae and the causality assigned was C2 (probable). There are also 15 reports on **oral** terbutaline, all indicated for asthma.

As for salbutamol, there are 7 reports on injectables and 37 reports on oral (tablet) products. None of these was indicated for tocolysis.

Regulatory Action

In its 205th meeting on 29 May 2008, DCA approved a policy paper submitted by MADRAC to impose a warning statement in the package insert of all injectable and oral (tablet and capsule only) beta agonist products. The statement warned about **incidence of myocardial ischaemia** in women receiving treatment with salbutamol and terbutaline for the treatment of preterm labour, although these products were not indicated for it.

In its 242th meeting on 28 July 2011, DCA again approved MADRAC's proposal to strengthen this warning. The statement that is to be incorporated into the package inserts is as follows:

WARNINGS & PRECAUTIONS

Tocolysis: *Serious adverse reactions including death have been reported after administration of terbutaline/salbutamol to women in labour. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased foetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.*

Reference:

1. FDA MedWatch. FDA Drug Safety Communication: New Warnings against use of terbutaline to treat preterm labor. http://www.fda.gov/Drugs/DrugSafety/ucm243539.htm [17 February 2011]

FLUOROQUINOLONES: EXACERBATION OF MYASTHENIA GRAVIS

The fluoroquinolone class of antibiotics may **exacerbate muscle weakness** in persons with myasthenia gravis. Patients with known history of myasthenia gravis are advised to avoid fluoroquinolones products. This safety information will be updated in the relevant package inserts in a timely manner. **Myasthenia gravis** is a chronic progressive disease characterised by fatigue and muscular weakness (especially in the face, neck, arms and legs), caused by impaired transmission of nerve impulses following an autoimmune attack of acetylcholine receptors.

Exacerbation of myasthenia gravis is a known but rare side effect of fluoroquinolone antibiotics. Post-marketing cases of serious adverse events, including deaths and requirement for ventilation support, have been associated with fluoroquinolone use in persons with myasthenia gravis. This safety alert concerns only **systemic** fluoroquinolones products (**oral and parenteral**). Products indicated for ophthalmic use are not affected.

Local Scenario

At present, there are 116 fluoroquinolone products registered in Malaysia. Drugs in the fluoroquinolone class include ciprofloxacin, lomefloxacin, norfloxacin, ofloxacin, pefloxacin, levofloxacin and moxifloxacin. Until August 2011, the National Centre of ADR Monitoring has received 289 reports related to fluoroquinolones. No report that can be associated with myasthenia gravis has been received.

Regulatory Action

In July 2011, MADRAC had proposed to update the package insert of all fluoroquinolone products with this safety information. The proposal was accepted by DCA in its 242nd meeting on 28 July 2011. New information that is to be added is as follows:

WARNINGS & PRECAUTIONS

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with flouroquinolones use in persons with myasthenia gravis. Avoid flouroquinolones in patients with known history of myasthenia gravis.

ADVERSE REACTIONS

Post Marketing Experience

Exacerbation of myasthenia gravis

Reference:

1. FDA MedWatch. Risk of fluoroquinolone-associated myasthenia gravis exacerbation: February 2011 label changes for fluoroquinolones. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm247115.htm [15 March 2011]

ANTIPSYCHOTIC DRUGS: CLASS LABELLING UPDATES ON USE DURING PREGNANCY & POTENTIAL RISK TO NEWBORNS

Package inserts for the entire class of antipsychotics drugs will be updated to include information about the potential risk for **abnormal muscle movements** (extrapyramidal signs, EPS) and **withdrawal symptoms** in **newborns** whose mothers were treated with these drugs during the third trimester of pregnancy.

The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing and difficulty in feeding.

Background

Through October 2008, 69 cases of neonatal EPS or withdrawal related to all antipsychotic drugs had been identified in the Adverse Event Reporting System (AERS) database of the US Food and Drug Administration (US FDA).

In these cases, blood levels were not provided, making it not possible to determine whether the events resulted from antipsychotic drug toxicity or withdrawal.

The onset of reactions ranged **from birth to one month after birth** and the symptoms varied in severity. In some newborns, the symptoms **subsided within hours or days** and did not require specific treatment, while others might **require intensive care unit support** and longer hospital stays.

Most cases were confounded by other factors, including concomitant use of other drugs known to be associated with withdrawal symptoms, prematurity, congenital malformations, as well as obstetrical and perinatal complications. However, there are some cases which suggest that neonatal EPS and withdrawal may occur with antipsychotics alone.

Local Scenario

There are 18 antipsychotic drugs (154 products) registered with the DCA. These are available in various dosage forms, i.e. tablet, capsule, oral solution as well as injection.

- Typical antipsychotics (59 products):
  chlorpromazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, haloperidol, flupenthixol/flupentixol, zuclopenthixol, sulpiride

- Atypical antipsychotics (95 products):
  amisulpride, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, aripriprazole

All substances, except sertindole, are listed in the Ministry of Health Drug Formulary.

Since 2000, the National Centre of ADR Monitoring has received 3 reports on drug exposure during pregnancy. Out of these reports, 2 were related to olanzapine and the remaining one reported on haloperidol.

	Suspected Drug	Effect on Mother	Effect on Neonate
1	Olanzapine	No ADR reported	Hypospadias, anotia
2	Olanzapine	Chorioamnionitis, premature rupture of membrane	Unknown (mother did not return for follow up)
3	Haloperidol	Hypokalaemia	No ADR reported

Vigisearch, the WHO ADR database, has received 75 reports of EPS or withdrawal symptoms related to antipsychotics in neonates.

Regulatory Action

In view of the importance of this information, MADRAC has proposed to include this risk into all relevant package inserts. The proposal was accepted by the DCA in its 240th meeting on 26 May 2011. The warning statement that is to be included is as follows:

PREGNANCY & LACTATION

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

[BRAND NAME] should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reference:

1. FDA MedWatch. Antipsychotic drugs: Class labeling change – Treatment during pregnancy and potential risk to newborns. http://www.fda.gov/Drugs/DrugSafety/ucm243903.htm [22 February 2011]

SAFETY ISSUES OF CURRENT INTEREST

BENZOCAINE TOPICAL PRODUCTS (SPRAYS, GEL & LIQUIDS): RISK OF METHAEMOGLOBINAEMIA

Post-marketing reports of **methaemoglobinaemia** with certain benzocaine topical products have been received by the US Food and Drug Administration (US FDA). These products include **sprays**, used during medical procedures to numb the mucous membranes of the mouth and throat; as well as **gels and liquids** used to relieve pain from a variety of conditions, such as teething, canker sores and irritation of the mouth and gums.

Methaemoglobinaemia is a rare but serious condition in which the amount of oxygen carried through the blood stream is greatly reduced. Signs and symptoms of methaemoglobinaemia include pale, gray or blue coloured skin, lips and nail beds, headache, lightheadedness, shortness of breath, fatigue and rapid heart rate. In the most severe cases, it can result in death.

Methaemoglobinaemia usually appears **within minutes to 1 or 2 hours** of applying benzocaine and may occur with **first application** (one-time use) or after additional use. This condition has been reported with **all strengths** of benzocaine gels and liquids, including concentrations as low as 7.5%. The cases occurred mainly in children aged 2 years or younger who were treated with benzocaine gel for teething.

Populations with **pre-disposing risk factors** for benzocaine-induced methaemoglobinaemia include: patients who have breathing problems, such as asthma, bronchitis or emphysema; patients with heart disease; patients who smoke; infants less than 4 months of age; elderly patients; patients with certain inborn defects, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency, haemoglobin-M disease, NADH-methaemoglobin reductase (diaphorase 1) deficiency and pyruvate-kinase deficiency; and patients who also use medications, foods and water containing nitrites and nitrates concurrently.

Local Scenario

There are 9 benzocaine-containing products registered in Malaysia, of which 2 are in **gel** form for oral use (Mucopain, Topicale). These are the only products containing benzocaine as the single active ingredient.

Benzocaine-containing products are also available as **lozenges** (Deqben, Horf, Pharmaniaga Cetylpyridinium B, Pharynx), **rectal ointment** (Doproct) and **suppository** (Doproct). Trolab, which is a plaster used in **patch test**, also contains benzocaine.

In Malaysia, all products listed above are categorised as **poison**. There is no OTC benzocaine product registered in Malaysia, unlike in the US where benzocaine gels and liquids are categorised as OTC products.

To date, the National Centre of ADR Monitoring has not received any report associated with the use of benzocaine products.

Literature showed that other local anaesthetics, such as lidocaine and prilocaine, may also cause methaemoglobinaemia. However, no report associated with topical use of these anaesthetics has been received.

Recommendations

Healthcare professionals are advised to adhere to the instruction in local package inserts, which contain the following statements:

DOSAGE & ADMINISTRATION

*Apply **small amount** evenly to the affected area.*

WARNINGS & PRECAUTIONS

***Methaemoglobinaemia** may rarely occur, particularly in infant and children, following application of large amounts, e.g. in pharyngeal anaesthesia.*
*Topical benzocaine should not be used in children below **2 years** / should be used in children below 2 years under the direction of dentist or physician.*
*It should not be used for **prolonged periods**.*

ADVERSE REACTIONS

*Rarely, benzocaine may induce methaemoglobinaemia causing **respiratory distress and cyanosis**.*

Teething pain in young children may be treated by giving the child a teething ring chilled in the refrigerator, or gently rubbing or massaging the child's gums with finger.

Reference:

1. FDA MedWatch. Benzocaine topical products: Sprays, gels and liquids – Risk of methaemoglobinaemia. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm250264.htm [7 April 2011]
2. MedEffect Canada. Health Canada reminds Canadians of health risks associated with topical benzocaine products. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_59-eng.php [20 April 2011]

NEWS & UPDATES

CERVARIX®: OVERVIEW OF THE NATIONAL IMMUNISATION PROGRAMME

According to Glaxo Smith Kline Sdn Bhd, the marketing authorisation holder for Cervarix®, a total of 874,368 doses (up to 19 April 2011) have been distributed to Malaysia since its registration in December 2007. Out of this total, 859,795 (98.3%) doses have been distributed as part of the Human Papillomavirus (HPV) National Immunisation Programme, which commenced in September 2010.

During monitoring of national use, Cervarix® generally demonstrated a favourable safety profile. No new risks have been identified for the vaccine and the benefits and risks ratio remains positive.

From the launching of the HPV National Immunisation Programme until March 2011, a total of 774 adverse event following immunisation (AEFI) reports have been received by the National Centre of ADR Monitoring. This calculates to a 0.09% reporting rate based on the number of doses distributed for this programme.

The majority of the reports received were non-serious and consistent with the expected pattern of adverse events for the vaccine, as described in the product package insert. Among the most commonly reported adverse events were application site disorders (i.e. injection site pain, injection site swelling/erythema) and central & peripheral nervous system disorders (i.e. dizziness, headache, giddiness). Other commonly reported symptoms include general disorders (i.e. weakness generalised, fever), gastrointestinal symptoms (i.e. nausea, vomiting) and musculoskeletal disorders (i.e. limb weakness).

In relation to the HPV National Immunisation Programme, two serious cases were reported in 2010. Adverse events reported include feeling cold, spasms and fits NOS. However, results of the investigations showed that the adverse reactions reported were not related to the vaccine and that there is no evidence for a safety signal.

At this time, reporters are still encouraged to report any expected, non-serious adverse effects experienced with Cervarix® using the simplified AEFI reporting form (as on the back cover of this issue), as well as any suspected, serious adverse reactions that are considered of concern using the usual reporting options (available on www.bpfk.gov.my). The National Centre of ADR Monitoring will continue to monitor national experience with use of Cervarix®, in the context of global safety data and any new safety information will be disseminated to all healthcare professionals once they are available.

BORANG PEMANTAUAN KESAN SAMPINGAN RINGAN SELEPAS PELALIAN

Pindaan-1

Pada kebiasaannya suntikan vaksin tidak menyebabkan kesan sampingan. Walaubagaimanapun sekiranya anda atau orang yang berada di bawah jagaan anda mengalami kesan sampingan selepas mendapat suntik an pelalian sila isi borang ini dan kembalikan kepada kakita ngan institusi kesihatan/sekolah tempat suntikan diberikan

1. Maklumat Penerima Vaksin : -
   a) Nama : .....
   b) Umur: ..... c) Jantina : ☐ Lelaki ☐ Perempuan
   d) Alamat : .....
   .....
   e) No. Tel : .....
   f) Bangsa : Melayu ☐ India ☐ Cina ☐ Lain-lain ☐ Nyatakan:.....
2. Tarikh suntikan diterima : .....
3. Jenis Vaksin :-
   a) Influenza A (H1N1) ☐
   b) Human Papillomavirus (HPV) ☐ Dos : pertama / kedua / ketiga *
   c) Lain – lain vaksin (vaksin) .....
4. Bahagian badan dimana vaksin disuntik : .....
5. Kesan Sampingan yang dialami: -
   (Tempoh masa di antara vaksin diterima dan kesan sampingan berlaku adalah penting untuk diisi)

Kesan Sampingan	Tandakan √ jika berkaitan	Tempoh masa berlaku selepas suntikan diterima (*pilih salah satu)
a. Kesan pada tempat suntikan :		
i) Bengkak	☐	.....minit/jam /hari *
ii) Sakit	☐	.....minit/jam /hari *
iii) Kegatalan	☐	.....minit/jam /hari *
iv) Merah pada tempat suntikan	☐	.....minit/jam /hari *
v) Lain-lain(nyatakan).....	☐	.....minit/jam /hari *
b. Demam	☐	.....minit/jam /hari *
c. Kesan alahan/ruam/gatal*	☐	.....minit/jam /hari *
d. Sakit otot/badan*	☐	.....minit/jam /hari *
e. Lesu badan	☐	.....minit/jam /hari *
f. Sakit kepala	☐	.....minit/jam /hari *
g. Pening kepala / loya / muntah*	☐	.....minit/jam /hari *
h. Lemah tangan / kaki*	☐	.....minit/jam/hari/minggu*
i. Lain-lain(nyatakan).....	☐	.....minit/jam /hari *

Sekiranya berlaku kesan sampingan yang serius, sila rujuk ke hospital yang berdekatan dengan segera.
Segala maklumat yang dikemukakan adalah sulit dan hanya akan digunakan untuk tujuan memantau kesan sampingan selepas pelalian sahaja.

Untuk Diisi Kakitangan Kesihatan

i. Maklumat vaksin digunakan :
   Jenama vaksin :..... No.Kelompok :..... Tarikh Luput : .....
ii. Maklumat Kakitangan Kesihatan Yang Menerima Laporan :-
   a) Nama : .....
   b) Cop/ Alamat tempat bertugas : .....
   .....
   c) No. telefon :..... Tarikh laporan :.....

Bagi kesan sampingan yang serius, anggota kesihatan perlu mengisi Borang Pelaporan Kesan Advers Ubat dan merujuk kepada Garispanduan Farmakovigilans Keselamatan Vaksin di Malaysia.

Sila majukan borang yang telah diisi dan sebarang pertanyaan atau aduan ke Biro Pengawalan Farmaseutikal Kebangsaan di talian 03-78835400 atau Faks 03-79567151