GlaxoSmithKline

Synflorix™

1. Name of the medicinal product

Synflorix™

Pneumococcal polysaccharide conjugate vaccine, adsorbed

2. Qualitative and quantitative composition

One dose (0.5 ml) contains 1 microgram of polysaccharide for serotypes 1[1,2], 5[1,2], 6B[1,2], 7F[1,2], 9V[1,2], 14[1,2] and 23F[1,2], and 3 micrograms of serotypes 4[1,2], 18C[1,3] and 19F[1,4].

[1] adsorbed on aluminium phosphate	0.5 milligram Al^{3+}
[2] conjugated to protein D (derived from Non-Typeable *Haemophilus influenzae*) carrier protein	~13 micrograms
[3] conjugated to tetanus toxoid carrier protein	~8 micrograms
[4] conjugated to diphtheria toxoid carrier protein	~5 micrograms

3. Pharmaceutical form

Suspension for injection in pre-filled syringe.

4. Clinical particulars

4.1 Therapeutic indications

Active immunisation against invasive disease and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 5 years of age.

The use of Synflorix should be determined on the basis of official recommendations taking into consideration the impact of invasive disease in different age groups as well as the variability of serotype epidemiology in different geographical areas.

4.2 Posology and method of administration

Posology

Infants from 6 weeks to 6 months of age:

Three-dose primary series

The recommended immunisation series to ensure optimal protection consists of four doses, each of 0.5 ml. The primary infant series consists of three doses with the first dose usually given at 2 months of age and with an interval of at least 1 month between doses. The first dose may be given as early as six weeks of age. A booster dose is recommended at least 6 months after the last priming dose and preferably between 12 and 15 months of age.

Two-dose primary series

Alternatively, when Synflorix is given as part of a routine infant immunisation programme, a series consisting of three doses, each of 0.5 ml may be given. The first dose may be administered from the age of 2 months, with a second dose 2 months later. A booster dose is recommended at least 6 months after the last primary dose.

Infants born between 27-36 weeks gestation

In preterm infants born after at least 27 weeks of gestational age, the recommended immunisation series consists of four doses, each of 0.5ml. The primary infant series consists of three doses with the first dose given at 2 months of age and with an interval of at least 1 month between doses. A booster dose is recommended at least 6 months after the last primary dose.

Previously unvaccinated older infants and children:

- **infants aged 7-11 months**: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 1 month between doses. A third dose is recommended in the second year of life with an interval of at least 2 months.
- **children aged 12-23 months**: The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses. The need for a booster dose after this immunisation schedule has not been established.
- **children aged 2– 5 years:** The vaccination schedule consists of two doses of 0.5 ml with an interval of at least 2 months between doses.

Official recommendations should be taken into account when immunising with Synflorix™.

It is recommended that subjects who receive a first dose of Synflorix™ complete the full vaccination course with Synflorix™.

Paediatric population: The safety and efficacy of Synflorix in children over 5 years of age have not been established.

Method of administration

The vaccine should be given by intramuscular injection. The preferred sites are anterolateral aspect of the thigh in infants or the deltoid muscle of the upper arm in young children.

4.3 Contra-indications

Synflorix™ should not be administered to subjects with known hypersensitivity to any component of the vaccine.

As with other vaccines, the administration of Synflorix should be postponed in subjects suffering from acute severe febrile illness. However, the presence of a minor infection, such as a cold, should not result in the deferral of vaccination.

4.4 Special warnings and special precautions for use

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Synflorix™ should under no circumstances be administered intravascularly or intradermally. No data are available on subcutaneous administration of Synflorix™.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

As for other vaccines administered intramuscularly, Synflorix™ should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Synflorix will not protect against pneumococcal serogroups other than those included in the vaccine. Although antibody response to diphtheria toxoid, tetanus toxoid and Protein D (protein D is highly conserved in all *Haemophilus influenzae* strains including NTHi) occurs, immunization with Synflorix does not substitute routine immunization with diphtheria, tetanus or *Haemophilus influenzae* type b vaccines.

Official recommendations for the immunisations against diphtheria, tetanus and *Haemophilus influenzae* type b should also be followed.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Safety and immunogenicity data in children with increased risk for pneumococcal infections (sickle cell disease, congenital and acquired splenic dysfunction, HIV-infected, malignancy, nephrotic syndrome) are not available.

Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunisation.

For children at high-risk for pneumococcal disease (such as children with sickle cell disease, asplenia, HIV infection, chronic illness or who are immunocompromised),

- the appropriate-for-age Synflorix vaccination series should be given below 2 years of age (*see Posology and method of administration*)
- a 23-valent pneumococcal polysaccharide vaccine should be given ≥ 2 years of age.

Prophylactic administration of antipyretics before or immediately after vaccines administration can reduce the incidence and intensity of post-vaccination febrile reactions. Data however, suggest that the use of prophylactic paracetamol might reduce the immune response to pneumococcal vaccines. The clinical relevance of this observation remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

4.5 Interaction with other medicaments and other forms of interaction

Use with other vaccines

Synflorix™ can be given concomitantly with any of the following monovalent or combination vaccines [including DTPa-HBV-IPV/Hib and DTPw-HBV/Hib]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), hepatitis B vaccine (HBV), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), diphtheria-tetanus-whole cell pertussis vaccine (DTPw), measles-mumps-rubella vaccine (MMR), varicella vaccine, meningococcal serogroup C conjugate vaccine (CRM_{197} and TT conjugates), oral polio vaccine (OPV) and rotavirus vaccine. Different injectable vaccines should always be given at different injections sites.

Clinical studies demonstrated that the immune responses and the safety profiles of the co-administered vaccines were unaffected, with the exception of the inactivated poliovirus type 2 response, for which inconsistent results were observed across studies (seroprotection ranging from 78% to 100%). The clinical relevance of this observation is not known. No negative interference was observed with meningococcal conjugate vaccines irrespective of the carrier protein (CRM_{197} and TT conjugates). Enhancement of antibody response to Hib-TT conjugate, diphtheria and tetanus antigens was observed. As with other vaccines it may be expected that in patients receiving immunosuppressive treatment an adequate response may not be elicited.

4.6 Use during pregnancy and lactation

As Synflorix™ is not intended for use in adults, adequate human data on use during pregnancy and lactation and adequate animal reproduction studies are not available.

4.7 Effect on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Clinical trials involved the administration of approximately 12,800 doses of Synflorix to approximately 4,500 healthy children and 137 preterm infants as primary vaccination. Furthermore, approximately 3,800 children and 116 preterm infants received a booster dose of Synflorix in the second year of life. Safety was also assessed in approximately 200 children from 2 to 5 years old. In all trials, Synflorix was administered concurrently with the recommended childhood vaccines.

No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the primary vaccination series.

An increase in injection site reactions was reported in children > 12 months of age compared to the rates observed in infants during the primary series with Synflorix.

Reactogenicity was higher in children receiving whole cell pertussis vaccines concomitantly.

The most common adverse reactions observed after primary vaccination were redness at the injection site and irritability which occurred after 38.3% and 52.3% of all doses respectively. Following booster vaccination, these adverse reactions occurred at 52.6% and 55.4% respectively. The majority of these reactions were of mild to moderate severity and were not long lasting.

Adverse reactions reported (for all age groups) are listed according to the following frequency:

Frequencies are reported as:

Very common:	(≥ 1/10)
Common:	(≥1/100 to <1/10)
Uncommon:	(≥1/1,000 to <1/100)
Rare:	(≥1/10,000 to <1/1,000)

Nervous system disorders:
Very common: drowsiness
Rare: febrile and non-febrile convulsions

Respiratory, thoracic and mediastinal disorders
Uncommon: apnoea in very premature infants (≤28 weeks of gestation)

Gastro-intestinal disorders:
Uncommon: diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Rare: rash, urticaria

Metabolism and nutrition disorders:
Very common: appetite lost

General disorders and administration site conditions:
Very common: pain, redness, swelling at the injection site, fever (≥38°C rectally) (age < 2 years)
Common: injection site induration, fever (>39°C rectally) (age < 2 years), fever ≥38°C rectally (age 2 to 5 years)
Uncommon: injection site haematoma, haemorrhage and nodule, fever (>40°C rectally)* (age < 2 years), fever >39°C rectally (age 2 to 5 years)

Immune system disorders
Rare: allergic reactions (such as allergic dermatitis, atopic dermatitis, eczema)

Psychiatric disorders:
Very common: irritability
Uncommon: crying abnormal
*reported following booster vaccination

4.9 Overdose

Insufficient data are available

5. Pharmacological particulars

5.1. Pharmacodynamic properties.

Synflorix™ is a pneumococcal polysaccharide conjugate vaccine using protein D as the main carrier protein. Protein D is a highly conserved surface protein from Non-Typeable *Haemophilus influenzae* (NTHi). The vaccine contains 10 *Streptococcus pneumoniae* serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F).

Epidemiological data

The 10 serotypes included in this vaccine represent the major disease-causing serotypes worldwide covering approximately 50% to 96% of invasive pneumococcal disease (IPD) in children <5 years of age.

Acute otitis media (AOM) is a common childhood disease with different etiologies. Bacteria are believed to be responsible for at least 60-70% of clinical episodes of AOM. *Streptococcus pneumoniae* and NTHi are the most common causes of bacterial AOM worldwide.

Efficacy against invasive pneumococcal disease:

The protective efficacy of Synflorix against IPD has not been studied. As recommended by WHO, the assessment of potential efficacy against IPD has been based on a comparison of immune responses to the seven serotypes shared between Synflorix and another pneumococcal conjugate vaccine for which protective efficacy was evaluated previously (i.e. 7-valent PCV vaccine). Immune responses to the extra three serotypes in Synflorix have also been measured.

In a head-to-head comparative trial with the 7-valent PCV vaccine, non inferiority of the immune response to Synflorix measured by ELISA was demonstrated for all serotypes, except for 6B and 23F (upper limit of the 96.5% CI around the difference between groups >10%).

For serotypes 6B and 23F, respectively, 65.9% and 81.4% of infants vaccinated at 2, 3 and 4 months reached the antibody threshold (i.e. 0.20 µg/ml) one month after the third dose of Synflorix versus 79.0% and 94.1% respectively, after three doses of the 7-valent PCV vaccine. The clinical relevance of these differences is not known.

The percentage of vaccinees reaching the threshold for the three additional serotypes in Synflorix (1, 5 and 7F) was respectively 97.3%, 99.0% and 99.5% and was at least as good as the aggregate 7-valent PCV vaccine response against the 7 common serotypes (95.8%).

Post-primary antibody geometric mean concentrations (GMCs) elicited by Synflorix against the seven serotypes in common were lower than those elicited by the 7-valent PCV vaccine. Pre-booster GMCs (8 to 12 months after the last primary dose) were generally similar for the two vaccines. After the booster dose the GMCs elicited by Synflorix were lower for most serotypes in common with the 7-valent PCV vaccine.

In the same study, Synflorix was shown to elicit functional antibodies to all vaccine serotypes. For each of the seven serotypes in common, 87.7% to 100% of Synflorix vaccinees and 92.1% to 100% of 7-valent PCV vaccinees reached an OPA (opsonophagocytic assay) titre ≥ 8 one month after the third dose. The difference between both vaccines in terms of percentage of subjects with OPA titres ≥ 8 was <5% for all serotypes in common, including 6B and 23F.

Post-primary and post-booster OPA antibody geometric mean titres (GMTs) elicited by Synflorix were lower than those elicited by the 7-valent PCV vaccine for the seven shared serotypes, except for serotype 19F.

For serotypes 1, 5 and 7F, the percentages of Synflorix vaccinees reaching an OPA titre ≥ 8 were respectively 65.7%, 90.9% and 99.6% after the primary vaccination course and 91.0%, 96.3% and 100% after the booster dose.

The OPA response for serotypes 1 and 5 was lower in magnitude than the response for each of the other serotypes. The implications of these findings for protective efficacy are not known. The response to serotype 7F was in the same range as for the seven serotypes in common between the two vaccines.

The administration of a fourth dose (booster dose) in the second year of life elicited an anamnestic antibody response as measured by ELISA and OPA for the 10 serotypes included in the vaccine demonstrating the induction of immune memory after the three-dose primary course.

It has also been demonstrated that Synflorix induces an immune response to the vaccine-related serotypes 6A and 19A. For these vaccine-related serotypes, 5.5 and 6.1 fold increases in geometric mean concentrations were observed respectively one month after a booster dose compared to pre-booster concentrations. In terms of GMT measured by OPA, 6.7 and 6.1 fold increases were observed respectively compared to pre-booster concentrations.

In a clinical study where infants were vaccinated at 6, 10, 14 weeks, the percentage of Synflorix vaccinees with antibody concentrations ≥ 0.20 µg/ml and with OPA titre ≥ 8 was in the same range as the percentage of 7-valent PCV vaccinees for the seven serotypes in common. The observed differences in the percentage of subjects with OPA titres ≥ 8 were below 5% for all serotypes except 19F (percentage was higher in the Synflorix group).

Efficacy against AOM:

In a large randomised double-blind Pneumococcal Otitis Media Efficacy Trial (POET), an 11-valent investigational vaccine (11Pn-PD) containing the 10 serotypes of Synflorix™ along with serotype 3, for which efficacy was not demonstrated, was given to 2,489 infants. In this study, the vaccine efficacy against AOM episodes was as follows:

Type or cause of AOM	Vaccine efficacy
Clinical AOM episodes regardless of etiology	33.6 % (95% CI: 20.8; 44.3)
AOM episodes due to any pneumococcal serotype	51.5% (95% CI: 36.8;62.9)
AOM episodes due to pneumococcal serotypes covered by the 11Pn-PD vaccine	57.6% (95% CI: 41.4;69.3)
AOM episodes due to pneumococcal serotypes covered by Synflorix™	67.9% (95% CI: 53.0;78.1)
AOM episodes due to vaccine related pneumococcal serotypes	65.5% (95 % CI: 22.4;84.7)
AOM episodes caused by Hi (including NTHi)	35.6% (95% CI: 3.8; 57.0)
AOM episodes caused by NTHi only	35.3% (95% CI: 1.8;57.4)

No increase in the incidence of AOM due to other bacterial pathogens was observed. The incidence of recurrent AOM (≥ 3 episodes in 6 months or ≥ 4 in 12 months) was reduced by 56% (95% CI:-1.9;80.7) and ventilation tube placement by 60.3% (95% CI:-6.7;87.5).

Based on immunological bridging of the functional vaccine response of Synflorix™ with the formulation used within POET, it is expected that Synflorix™ provides similar protective efficacy against pneumococcal AOM.

Preterm infants

Immunogenicity of Synflorix in very preterm (born after a gestation period of 27-30 weeks) (N=42), preterm (born after a gestation period of 31-36 weeks) (N=82) and full term (born after a gestation period of more than 36 weeks) (N=132) infants was evaluated following a three dose primary vaccination course at 2, 4, 6 months of age. Immunogenicity was evaluated in 44 very preterm, 69 preterm and 127 full term infants following a booster dose at 15 to 18 months of age. Regardless of maturity, one month after primary vaccination, at least 92.7% of subjects achieved ELISA antibody concentrations ≥ 0.2 µg/ml and at least 81.7% achieved OPA titres ≥ 8 for all vaccine serotypes, except serotype 1 (at least 58.8% with OPA titres ≥ 8). Similar antibody GMCs and OPA GMTs were observed for all infants except lower antibody GMCs for serotypes 4, 5 and 9V in very preterms and serotype 9V in preterms and lower OPA GMT for serotype 5 in very preterms. Increases of ELISA antibody GMCs and OPA GMTs were seen for all serotypes one month after the booster dose, indicative of immunological memory. Similar antibody GMCs and OPA GMTs were observed for all infants except a lower OPA GMT for serotype 5 in very preterm infants. Overall, at least 97.6% of subjects achieved ELISA antibody concentrations ≥ 0.2µg/ml and at least 91.9% achieved OPA titres ≥ 8 for all vaccine serotypes.

Protein D immune responses post-primary and booster vaccination were similar for very preterm, preterm and full term infants.

2-dose primary schedule

In addition to the 3-dose primary schedule, the immunogenicity of Synflorix following a 2-dose primary vaccination schedule in subjects less than 6 months of age was evaluated in two clinical studies.

In the first study, the immunogenicity two months after the second dose of Synflorix was compared with a 7-valent PCV vaccine and the percentages of subjects with ELISA antibody concentration ≥ 0.2 mg/ml were within the same range for each of the serotypes common to both vaccines with the exception of serotypes 6B (64.1% for Synflorix and 30.7% for the 7-valent PCV vaccine), and 18C (87.1% for Synflorix and 97.6% for the 7-valent PCV vaccine). Antibody GMCs were similar in both groups, with the exception of serotypes 6B (0.34 µg/ml, for Synflorix and 0.16 µg/ml for the 7-valent PCV vaccine) and 4, 9V and 18C (1.23 µg/ml, 0.92 µg/ml, 1.21µg/ml respectively for Synflorix and 2.02 µg/ml, 2.24 µg/ml, 1.79 µg/ml respectively for the 7-valent PCV vaccine). Similarly, the percentage of subjects reaching OPA titres ≥ 8 and the OPA GMTs two months post dose 2 was within the same range for each of the serotypes common to both vaccines, with the exception of serotypes 6B and 19F for which responses were higher in the Synflorix vaccinees group (OPA GMTs of 94.2 for Synflorix versus 22.8 for 7-valent PCV vaccine for serotype 6B; 65.8 for Synflorix versus 19.3 for 7-valent PCV vaccine for serotype 19F).

In the second study, the immunogenicity after two doses of Synflorix was compared to three doses of Synflorix. Although there was no significant difference between the two groups in the percentages of subjects with antibody concentration ≥ 0.2µg/ml (ELISA), a lower percentage of subjects with OPA titers ≥ 8 in 2-dose primed subjects compared to 3-dose primed subjects was observed for serotypes 6B, 18C and 23F *(74.4%, 82.8%, 86.3% respectively for the 2-dose schedule and 88.9%, 96.2%, 97.7% respectively for the 3-dose schedule)*. In both schedules, a booster response indicative of immunological priming was observed for each serotype. Following the booster, a lower percentage of subjects with OPA titers ≥ 8 was observed with the 2+1 schedule for serotype 5 *(87.2% for the 2+1 schedule and 97.5% for the 3+1 schedule)*. While the clinical relevance of these observations remains unknown, the persistence of the immune response was evaluated in a follow-up of this second study.

In the follow-up of the second study, the persistence of antibodies at 36-46 months of age was demonstrated in 2-dose primed subjects with at least 83.7% of subjects remaining seropositive for vaccine serotypes (i.e. detectable antibody ≥ 0.05 mg/ml) of which serotypes 5, 7F, 9V, 14, 18C and 19F had at least 96.0% of subjects seropositive. A single dose of Synflorix administered during the 4th year of life, as a challenge dose, elicited higher ELISA antibody GMCs 7-10 days following vaccination in 2-dose primed subjects (ranging from 4.00 to 20.28 µg/ml) and 3-dose primed subjects (ranging from 4.72 to 30.55 µg/ml) compared to unprimed subjects (ranging from 0.10 to 2.37 µg/ml). This was indicative of an anamnestic immune response in primed subjects for all vaccine serotypes. The fold increase in ELISA antibody GMCs and OPA GMTs, pre to post vaccination, in 2-dose primed subjects was similar to that in 3-dose primed subjects.

For the vaccine-related serotypes 6A and 19A, induction of immune memory was demonstrated. For serotype 6A, a 4 fold-increase in ELISA GMCs was observed for both 2-dose and 3-dose primed subjects and for OPA GMTs, a 25 fold and a 15 fold-increase were observed in the 2 dose and the 3 dose primed subjects respectively. In unprimed subjects, there was a 1.4 fold increase in antibody GMCs and a 11 fold increase in OPA GMTs. For serotype 19A, a 11 fold and a 14 fold increase in ELISA GMCs were observed in the 2 dose and the 3 dose primed subjects respectively while for OPA GMTs, a 99 fold and a 217 fold increase were observed in 2-dose and 3-dose primed subjects respectively. In unprimed subjects, there was a 2.5 fold increase in antibody GMCs and a 39 fold increase in OPA GMTs.

A 3-dose primary schedule has shown higher antibody response against protein D compared to a 2-dose primary schedule. Anamnestic immune responses to protein D were shown with both schedules. However, the clinical relevance of these observations remains unknown.

5.2 Pharmacokinetic properties

Evaluation of pharmacokinetic properties is not required for vaccines.

5.3 Preclinical safety data

A repeated dose toxicity study of pneumococcal conjugate vaccine in rabbit revealed no evidence of any significant local or systemic toxic effects.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride, water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the vaccine is indicated on the label and packaging.

6.4 Special precautions for storage

Store at +2°C to +8°C (in a refrigerator).
Do not freeze.
Store in the original packaging in order to protect from light.
Not all pack sizes may be marketed.

6.5 Nature and contents of container

Synflorix™ is presented:
- in pre-filled syringes for 1 dose (0.5 ml) with a plunger stopper (rubber butyl) with or without needles. Pack sizes of 1 or 10.
- in vials for 1 dose (0.5 ml) with a stopper (rubber butyl). Pack sizes of 1, 10 or 100.
- in vials for 2 doses (1 ml) with a stopper (rubber butyl). Pack size of 100.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to US Pharmacopoeia requirements

6.6 Instructions for use, handling and disposal (if appropriate)

A fine white deposit with a clear colourless supernatant may be observed upon storage of the syringe/vial. This does not constitute a sign of deterioration.

The content of the syringe/vial should be inspected visually both before and after shaking for any foreign particulate matter and/or abnormal physical appearance prior to administration.

In the event of either being observed, discard the vaccine.

The vaccine should be well shaken before use.

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

For further information, please contact the manufacturer.

Synflorix is a trademark.

ان هذا الدواء:
الدواء مستحضر يؤثر على صحتك واستهلاكه خلافاً للتعليمات يعرضك للخطر.
اتبع بدقة وصفة الطبيب وطريقة الاستعمال المنصوص عليها وتعليمات الصيدلاني الذي صرفها لك.
– فالطبيب والصيدلاني هما الخبيران بالدواء وبنفعه وضرره.
– لا تقطع مدة العلاج المحددة لك من تلقاء نفسك.
– لا تكرر صرف الدواء بدون وصفة طبية.
– لا تترك الأدوية في متناول أيدي الأطفال.
مجلس وزراء الصحة العرب
واتحاد الصيادلة العرب.

THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists.

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