Annex II

Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Priorix and associated names (see annex I)

Priorix is a combined freeze-dried measles (M), mumps (M), and rubella (R) vaccine (live) preparation. The pharmaceutical form and strength is identical in all countries. The vaccine is a lyophilised vaccine preparation, which is reconstituted with separately supplied sterile diluent (water for injection) prior to use.

Priorix is nationally approved in 20 countries and is approved through the mutual recognition procedure (MRP) in 9 countries. The summary of product characteristics (SmPC) adopted in the member states in the MRP and the member states in the national procedures are slightly different. The purpose of this Art 30 referral is to harmonise the SmPC across EU member states for Priorix and associated names.

- **Clinical aspects**

In general, the MAH proposed a harmonised text drafted mainly using as basis the one approved in the MRP procedure with some amendments. In addition, the product information (PI) was presented using the latest version of the QRD template, version 2, published on 12 October 2011.

Section 4.1 – Therapeutic indications

Priorix is indicated for the active immunisation against measles, mumps and rubella. The approved lower age limit indicated for the use of Priorix varied from 9 months to 15 months across the individual EU member states reflecting in some cases the national recommendations for routine MMR vaccination.

The immunogenicity of Priorix was evaluated in several clinical trials in children aged from 12 to 24 months, 11 to 23 months and 9 to 12 months.

Based on the assessment of all data, the Marketing Authorisation Holder (MAH) proposed to align the indication of Priorix to children aged from 9 months old using the following wording: *"PRIORIX is indicated for the active immunisation of children from the age of 9 months or older, adolescents and adults against measles, mumps and rubella."*

The CHMP noted that recent data from an outbreak in France indicate that the highest incidence of measles infections was observed in infants below 1 year of age, followed by children between one and two years old. The incidence rates among the cases in both these age categories were above 50 and 45 cases per 100,000 respectively. Compared with 2009, the number of cases in 2010 more than tripled in infants below one year of age, and increased fivefold in adults 20-29 years old. Of the notified cases in 2010, almost 30% were hospitalized and a higher severity of the disease was observed in infants under one year of age and adults above 20 years, with respective proportions of hospitalised cases of 38% and 46%.Vaccination of children from 9 months onwards is therefore one tool to contain such outbreaks.

The immunogenicity data however clearly demonstrate that lower antibody responses against measles and mumps are observed in children aged 9 to 11 months at the time of primary immunization than in older children which is most likely due to circulating maternal antibodies or the immaturity of the immune system. Therefore a second dose given preferable 3 months after

the first dose is mandatory in this age group to ensure appropriate protection against measles, mumps and rubella.

In conclusion, based on the clinical data the lower age limit of the indication is endorsed, however since the immune response following a single dose of Priorix is lower in children under 12 months of age a reference to sections 4.2, 4.4 and 5.1 has been included. More specifically: "*For use in children between 9 to 12 months of age see sections 4.2, 4.4 and 5.1.*"

The MAH had also included in this section the sentence "*The use of PRIORIX should be based on official recommendations.*" but the CHMP agreed to move it at the beginning of section 4.2 Posology and method of administration because as per the guideline on SmPC dated September 2009 the reference to official recommendations should be made under section 4.2.

Section 4.2 - Posology and method of administration

For all countries, the dose of reconstituted Priorix vaccine is 0.5 ml. The method of administration of Priorix is subcutaneous injection, although it can also be given by intramuscular injection. The intramuscular route of administration is approved in all Member States except The Netherlands. The MAH also proposed to add a specific sub-section on the paediatric population as per the SmPC guideline.

The CHMP agreed that the dosing recommendations are acceptable, however in order to provide clear instructions to health care professionals a more structured wording was proposed (i.e. to split the recommendations per age group).

As regards the intramuscular route of administration no information was provided in the updated clinical dossier, but was provided in the initial application for marketing authorisation. The intramuscular route of administration was initially investigated in a small number of subjects (N=40) with seroconversion rates of 96.7%, 97.5% and 100% against measles, mumps and rubella, respectively. The geometric mean titers (GMTs) for seroconverters were 2431.9 mIU/ml, 1010.0 U/ml and 67.1 IU/ml for the anti-measles, anti-mumps and anti-rubella antibodies, respectively which were slightly lower than the values reported following subcutaneous administration (2958 mIU/ml, 1400 U/ml and 73 IU/ml, respectively). Although there are only limited data, it was noted that intramuscular administration is standard practice in many Member States. In addition experiences with other MMR or MMRV (measles, mumps, rubella, varicella) vaccines do not indicate any negative impact on the immune response or safety profile following intramuscular injection. For patients with thrombocytopenia or any coagulation disorder subcutaneous administration is recommended and thus a statement has been included.

Section 4.3 - Contraindications

Subjects with immune deficiencies

The major divergence in the approved SmPCs relates to the administration of Priorix in HIV-infected subjects. Systematic reviews on the safety, immunogenicity and efficacy of measles vaccination in children infected with HIV revealed that attenuated measles vaccine virus can caused severe complications or fatal disease in severely immunosuppressed HIV-infected patients. Moreover the antibody response to measles vaccine decreases as the level of immunosuppression increases. An association between lack of measles-specific antibodies after vaccination and low CD+ T-lymphocyte counts (<600cells/mm^3) was reported in published studies (Moss et al. 2003).

In HIV infected children with no evidence of immunosuppression measles vaccine has been safe and the risk of vaccine induced virus disease is very low. Given the severe course of wild type measles infection in patients with advanced HIV infection, it is recommended by the World Health

Organisation (WHO) to routinely vaccinate potentially susceptible, asymptomatic HIV positive children and adults.

Mumps and rubella vaccine viruses have not been recognized to cause serious complications in HIV-infected persons, but as they are unlikely to benefit and complications could occur severely immunocompromised persons should not be vaccinated.

The CHMP was of the opinion that the statement on subjects with humoral and cellular deficiency was appropriate and in line with the approved contraindication of other MMR vaccines. As regards HIV, there is no common European guidance on the CD4+ classification for % CD4+ or the cell count number. The WHO classification of HIV-related disease in adults and children published in 2006 states the following:

"*Immunological criteria for diagnosing advanced HIV in a child younger than five years of age with severe HIV infection:*

%CD4+ <25 among those younger than 12 months

%CD4+ <20 among those aged 12–35 months

%CD4+ <15 among those aged 36–59 months"

In addition there are reports of measles inclusion-body encephalitis following MMR vaccination in children with primary immunodeficiency and dysgammaglobulinemia (see Bitnun et al. 1999 Clin. Infect Dis).

In summary, the CHMP supported the proposal of the MAH which was "*Humoral or cellular immune deficiency (primary or acquired), including hypogammaglobulinaemia, dysgammaglobulinaemia and AIDS or symptomatic HIV infection or an age-specific CD4+ T-lymphocyte percentage <25%"*. However, it was considered necessary to include age specific %CD4+ as per WHO guidance since vaccination of children from the age of 9 months onwards is indicated.

The CHMP also noted that the contraindication for immune-depressed humans might need a general rewording in all MMR vaccines following the progress of science and the important knowledge of the immunology. This might need to be reviewed for all concerned products.

Pregnancy

Priorix is contraindicated in pregnant women. During the CHMP discussion it was questioned whether "pregnancy" should continue to be stated under contraindications. In order to get more insight in possible harm of MMR vaccination during pregnancy or pre-conception the CHMP asked from the MAH to provide evidence from enhanced surveillance and controlled studies that focus on risk of spontaneous abortion in women susceptible to measles, mumps and/or rubella, risk of malformation and congenital rubella syndrome (CRS) in offspring of such women, follow-up data up to 1 year age of children born from rubella susceptible women.

As Priorix is contraindicated in pregnant women neither interventional nor active surveillance activities have been set up. The data set provided by the MAH was generated by post-marketing data from the MAH's safety database and data from recent published literature about MMR vaccination in pregnant women. The data from spontaneous reports and the pregnancy registry have not indicated a safety concern with respect to spontaneous abortion or congenital malformations related to the inadvertent administration of Priorix in pregnant women. However, it was noted by the MAH that the data are very limited considering the contraindication currently in the label.

Natural rubella infection can have a devastating impact on pregnancy, leading to foetal death, premature delivery and an array of congenital defects. Approximately 85% of pregnancies will be negatively affected when rubella infection occurs during the first trimester. The attenuated virus

strain in the current rubella vaccine can rarely infect the foetus and there is no evidence that foetal infection with the vaccine virus is harmful. The theoretical maximum risk for CRS after administration of the vaccine at 1.6%, is much lower than the risk of major non-CRS induced congenital defects during pregnancy (Bozzo et al., 2011).

Though available data in the literature highlight a valuable perspective with regard to the overall risk of vaccine exposure at various stages of pregnancy, the theoretical risk, and because it is impossible to prove that the risk is zero, the MAH proposed that known pregnancy remains a contraindication to administration of rubella-containing vaccine.

The CHMP noted that since vaccination of measles, mumps rubella vaccine is generally contraindicated in pregnant women only limited data of spontaneous abortion, malformations and congenital rubella syndrome in the offspring following vaccination with Priorix are available. Review of pharmacovigiliance and published data does not indicate a risk of CRS in inadvertently vaccinated women, who are pregnant or conceived shortly after vaccination with Priorix. Published data from women of childbearing age that were vaccinated in the region of Central and South America demonstrate no or a negligible risk (0-0.2%) for CRS following vaccination of unknowingly pregnant women with a rubella containing vaccine. The theoretical teratogenic risk following rubella vaccination has been estimated to be 0.5% during the first trimester and is up to 1.6%, if the vaccine is given between 1-2 weeks before and 4-6 weeks after conception. Because of this theoretical teratogenic risk, the WHO recommended in 2011 that rubella vaccination of pregnant women should be avoided in principle, and women who intend to become pregnant should be advised to delay for 1 month following rubella vaccination. As there is still a theoretical teratogenic risk connected to rubella containing vaccines it was agreed that this very vulnerable group should not be put at risk.

In conclusion, the CHMP was of the opinion that the statement of "pregnancy" as a contraindication was in line with the approved contraindication of other MMR vaccines. There is currently no information to conclude that there is a teratogenic risk following vaccination with MMR vaccines however the theoretical concern remains. The risk for measles vaccination (enhancement of spontaneous abortion of stillbirth) is indicated to be unknown.

The CHMP also noted that there are some published data at present that could justify the lifting of the absolute contraindication for pregnant women from MMR vaccines as it is believed that although the vaccination of pregnant women is not recommended, in some individual cases the benefit of vaccination of a pregnant woman might outweigh the risk. This might need to be reviewed for all concerned products.

Section 4.4 - Special warnings and precautions for use

To be in line with the SmPC guideline the company proposed to:

- reduce a long paragraph about the use of epinephrine by a general statement about the availability of appropriate medical treatment and supervision following the administration of the vaccine.
- adapt the wording about HIV+ subjects and hypersensitivity to vaccine components to align with section 4.3.
- delete wording about age of vaccination (covered in section 4.2)

The Company also suggested rephrasing the paragraph about the idiopathic thrombocytopenic purpura (ITP).

The CHMP recommended reordering of some of the statements and adding subtitles to clearly distinguish each precaution (i.e. thrombocytopenia, immunocompromised patients, and transmission).

Since no immunogenicity data are available on the influence of the prophylactic use of antipyretics it was recommended that the paragraph on administration of Priorix to individuals with Central

Nervous System (CNS) disorders be reworded as follows "*Due caution should be employed in administration of PRIORIX to individuals with Central Nervous System (CNS) disorder, susceptibility to febrile convulsions or family history of convulsions. Vaccinees with a history of febrile convulsions should be closely followed-up.*"

The CHMP agreed that the sentence regarding fructose intolerance should change from "*Patients with rare hereditary problems of fructose intolerance should not take this medicine.*" to "*Patients with rare hereditary problems of fructose intolerance should not be vaccinated with PRIORIX since it contains sorbitol*".

It was decided to delete the statement on pregnancy from 4.4 because according to the guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labeling (EMEA/CHMP/203927/200), reference to pregnancy should only be made in section 4.3 and 4.6.

Because of the much higher likelihood of thrombocytopenia after natural infection, the benefits of vaccination most often exceed the risks of severe symptomatic thrombocytopenia caused by immunization. The CHMP therefore suggested adding the information from a recent systematic review that "*MMR-associated thrombocytopenia is rare and generally self-limited*". Also for clarity, the CHMP agreed to replace the company's proposal "*In such cases, the risk-benefit of immunising with Priorix should be carefully evaluated*" by "*Patients with existing thrombocytopenia or a history of thrombocytopenia after measles, mumps or rubella vaccination should be immunized with caution*"

The MAH slightly modified the proposed text and the final wording agreed by the CHMP is:

"*Cases of worsening of thrombocytopenia and cases of recurrence of thrombocytopenia in subjects who suffered thrombocytopenia after the first dose have been reported following vaccination with live measles, mumps and rubella vaccines. MMR-associated thrombocytopenia is rare and generally self-limited. In patients with existing thrombocytopenia or a history of thrombocytopenia after measles, mumps or rubella vaccination the risk-benefit of administering PRIORIX should be carefully evaluated. These patients should be vaccinated with caution and preferably using subcutaneous route*".

The paragraph on immunosuppression proposed by the MAH was considered outdated by the CHMP and a rewording was proposed. The MAH accepted the new text and also added a sentence on the monitoring of those patients which was endorsed by the CHMP. The final agreed wording is:

"*Immunocompromised patients who have no contraindication for this vaccination (see section 4.3) may not respond as well as immunocompetent patients, therefore some of these patients may acquire measles, mumps or rubella in case of contact, despite appropriate vaccine administration. These patients should be monitored carefully for signs of measles, parotitis and rubella.*"

Regarding the paragraph on transmission the proposal of the MAH was considered in principle acceptable by the CHMP with the addition that not only rubella but also measles pharyngeal excretion is known to appear. The MAH amended the corresponding part accordingly and also added another sentence to reflect the documented transplacental transmission. This was endorsed by the CHMP. The final agreed wording is:

"*Transmission of measles and mumps virus from vaccinees to susceptible contacts has never been documented. Pharyngeal excretion of the rubella and measles virus is known to occur about 7 to 28 days after vaccination with peak excretion around the 11th day. However there is no evidence of transmission of these excreted vaccine viruses to susceptible contacts. Transmission of the rubella vaccine virus to infants via breast milk as well as transplacental transmission has been documented without any evidence of clinical disease.*"

Section 4.5 – Interactions with other medicinal products and other forms of interaction

Clinical studies demonstrated that Priorix can be administered concomitantly with live attenuated varicella vaccine, DTPa-IPV and combined hepatitis A/B vaccine (Marshall et al., 2006; Stuck et al., 2002; Usonis et al., 2005; Wellington and Goa, 2003). More recently Priorix has been co-administered with Haemophilus influenzae type b (Hib) and meningococcal C conjugate vaccines as well as with concomitant co-administration with hepatitis A inactivated vaccine and pneumoccocal 7-valent conjugate vaccine. The data available do not suggest any clinically relevant interference in the antibody response to each of the individual antigens (Carmona et al., 2010; Pace et al., 2008).

Some vaccines that can be co-administered with Priorix are listed in the SmPC of Belgium, Bulgaria, Cyprus, Denmark, Estonia, France, Luxemburg, Malta, The Netherlands, Poland, Romania and United Kingdom. The MAH proposed to use a general sentence and not to list the different vaccines.

The CHMP noted that for the majority of clinical trials investigating co-administration of Priorix with other vaccines no CSRs are available but only literature references. The available data do not suggest that co-administration of these vaccines has an impact on the immunogenicity and safety of the antigens tested. However, since new and very complex childhood vaccines are under development it was recommended to list vaccines applicable for co-administration rather than to give a general statement on co-administration with other vaccines.

The MAH amended this paragraph as per the CHMP's recommendation and also added in the list one more vaccine (10-valent pneumococcal conjugate vaccine). This was endorsed by the CHMP following review and assessment of the clinical study report that was submitted to support the co-administration of Priorix with this vaccine. The final agreed wording is:

"*PRIORIX can be given simultaneously (but at separate injection sites) with any of the following monovalent or combination vaccines [including hexavalent vaccines (DTPa-HBV-IPV/Hib)]: diphtheria-tetanus-acellular pertussis vaccine (DTPa), Haemophilus influenzae type b vaccine (Hib), inactivated polio vaccine (IPV), hepatitis B vaccine (HBV), hepatitis A vaccine (HAV), Meningococcal serotype C conjugated vaccine (MenC), varicella zoster vaccine (VZV), oral polio vaccine (OPV) and 10-valent pneumococcal conjugate vaccine in accordance with local recommendations. If not given at the same time, an interval of at least one month is recommended between administration of PRIORIX and other live attenuated vaccines. There are no data to support the use of PRIORIX with any other vaccines.*"

With regard to the delay of vaccination in subject who have received human gammaglobulins or a blood transfusion the CHMP was of the opinion that a longer interval between immunoglobulin or other blood product and subsequent vaccination is recommended in case of administration of high dose such as the one given in patients with Kawasaki Disease (2g/kg). The wording of this paragraph was amended as follows: "*In subjects who have received human gammaglobulins or a blood transfusion, vaccination should be delayed for three months or longer (up to 11 months) depending on the dose of human globulins administered because of the likelihood of vaccine failure due to passively acquired measles, mumps and rubella antibodies*".

Section 4.6 – Fertility, pregnancy and lactation

Fertility

The sentence was modified as per the QRD recommendation to read "*PRIORIX has not been evaluated in fertility studies*".

Pregnancy

Priorix is contraindicated in pregnancy but since there is currently no information to conclude that there is a teratogenic risk following vaccination with MMR vaccines the following wording was

agreed: "*PRIORIX is contraindicated during pregnancy (see section 4.3). However foetal damage has not been documented when measles, mumps and rubella vaccines have been given to women who were unknowingly in early stages of pregnancy*".

Women of Childbearing Potential

In the SmPC of Bulgaria, Cyprus, Estonia, Malta and the United Kingdom, it is stated that pregnancy must be avoided for one month after vaccination as compared to the three months in the SmPC of the countries involved in the MRP and other countries. The Advisory Committee on Immunization Practices (ACIP) shortened its recommended period in 2001 to avoid pregnancy after receipt of rubella-containing vaccine from 3 months to 28 days because no case of CRS had been identified among infants born to women who were vaccinated inadvertently against rubella within 3 months or early in pregnancy (Center for Disease Control and Prevention, 2001). However, since studies have not been conducted with Priorix in pregnant women the MAH proposed that pregnancy should be avoided 3 months after vaccination.

The CHMP noted that because of this theoretical teratogenic risk, the WHO recommended in 2011 that rubella vaccination of pregnant women should be avoided in principle, and women who intend to become pregnant should be advised to delay for 1 month following rubella vaccination. To be in line with current WHO recommendations the CHMP was of the opinion that delay in pregnancy should be changed from 3 months to 1 month after vaccination.

The final agreed wording is: "*Women who intend to become pregnant should be advised to delay for 1 month following PRIORIX vaccination. Although women should be asked about the possibility of early pregnancy prior to vaccination, screening tests to exclude pregnancy are not required. Inadvertent vaccination of unknowingly pregnant women with PRIORIX should not be a reason for termination of pregnancy*".

Breast-feeding

The MAH stated that there is insufficient experience in the use of Priorix in breastfeeding women and that vaccination of breastfeeding women can be considered if the benefit of vaccination outweighs the risk.

The CHMP noted that there are no theoretical risks of vaccination during breastfeeding. Even if vaccine virus is transmitted, the infection is mild and self-limiting (ACIP 2011). It was therefore suggested to change the content of the paragraph accordingly. Vaccination of breastfeeding women with measles, mumps or rubella vaccines has not been related with any safety problem for the women or their infants, although there is limited experience with Priorix during breastfeeding. Only if the child is confirmed or suspected to be immunodeficient, risks and benefits of vaccinating its lactating mother should be outweighed. In addition it was stated that the advice on breastfeeding should be clearer with respect to the different recommendations for vaccinating mothers with children with or without immunodeficiency.

The MAH implemented all comments made by the CHMP and the final agreed wording was: "*There is limited experience with PRIORIX during breast-feeding. Studies have shown that breast-feeding postpartum women vaccinated with live attenuated rubella vaccines may secrete the virus in breast milk and transmit it to breast-fed infants without evidence of any symptomatic disease. Only in the event the child is confirmed or suspected to be immunodeficient, risks and benefits of vaccinating the mother should be evaluated (see section 4.3)*".

Section 4.8 - Undesirable effects

The main divergences between the proposed harmonized SmPC and national product information relates to the description of post marketing reports. In order to comply with the SmPC guideline

the MAH proposed a list of the adverse reactions in line with the MedDRA system organ classification. In addition the MAH proposed to delete the wording about comparative studies that demonstrated a statistically significant lower incidence of pain, redness and swelling at the injection site with Priorix compared to the reference product (Ipp *et al.*, 2004; Ipp *et al.*, 2006; Knutsson *et al.*, 2006; Taddio *et al.*, 2009; Wellington and Goa, 2003). Accordingly to the SmPC guideline, the SmPC provides information on a particular medicinal product; therefore it should not include reference to other medicinal products.

The CHMP agreed that the list of adverse reactions reported from clinical trials and post marketing experience was appropriately reflected in the proposed harmonized SmPC. The MAH was however asked to consider restructuring section 4.8 in accordance with the SmPC guideline to provide clear and readily accessible information (summary of the safety profile, tabulated list of adverse reactions, description of selected adverse reactions).

In addition as there was one inconsistency with the package leaflet the MAH was asked to add "*atypical mild or attenuated measles*" in section 4.8 under infections and infestations. Moreover, in the reference note for encephalitis the MAH was asked to add the risk of encephalitis after mumps infection, "*mumps: 2-4 in 1000 cases*". Finally, the wording "*adverse events*" was replaced by "*adverse reactions*" in all the section as per the QRD comments.

The MAH performed all the above changes but in order to be consistent with the SmPCs of all GSK vaccines the MAH asked to continue presenting adverse reactions as a list keeping a separation between the adverse reactions reported in clinical trials and the adverse reaction reported in post-marketing. This justification was accepted by the CHMP.

Section 5.1 – Pharmacodynamic properties

According to the SmPC guideline, the text should not include reference to other medicinal products, so the MAH proposed to delete reference on the result of comparative studies that were present in the SmPC of some MSs.

The CHMP noted that the current clinical experience with Priorix is limited to children and no trials were performed in adolescents and adults. Therefore, a statement should be added on the use in adolescents and adults.

The MAH was asked to consider adding a specific overview of immunogenicity assessment in infants vaccinated at an age below 12 months, with month-specific figures if available, for a first dose, as well as an overview of the assessment of an early second dose. For this reason and to reflect the most recent information, the immunogenicity data were differentiated between two groups: "*Immune response in children 12 months and older*" and "*Immune response in children aged 9 to 10 months*".

The MAH was asked to consider adding an overview of vaccine immunogenicity assessment (clinical trials), and to add vaccine efficacy figures as well, if available, or to mention their inexistence. A seropositive response by ELISA may not necessarily represent protection, especially for mumps. Vaccine efficacy data should differentiate between one or two doses. In the past decade, several mumps outbreaks have been reported in highly vaccinated populations (two doses). A number of studies documented increased risk of developing mumps with increasing time after vaccination (Vandermeulen et al., 2004; Cortese et al., 2008; Castilla et al., 2009), and data from the United Kingdom indicate vaccine effectiveness may decrease with age, which probably also reflects increasing time from vaccination (Cohen et al., 2007). Mumps vaccine efficacy has also been suggested to be lower in high-transmission settings (Brockhoff 2004). The MAH was asked to add some information on this issue. However, none of the field (outbreak) studies provided by the MAH

gave data specific for Priorix. So, there were no Priorix-specific data on mumps effectiveness and the general comments proposed by the MAH were endorsed by the CHMP.

Finally, the CHMP asked the seroconversion rates given to be replaced by more recent data reported for the Human Serum Albumin-free (HSA-free) formulation of Priorix and also asked the MAH if there are any immunogenicity data available from the Human Serum Albumin-free (HSA-free) formulation in children below 12 months of age. The MAH replaced the seroconversion rates and stated data from children below 12 months of age are yet to come as a study is currently being conducted.

Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the scope of the referral was the harmonisation of the summary of products characteristics, labelling and package leaflet
- the summary of products characteristic, labelling and package leaflet proposed by the marketing authorisation holder(s) have been assessed based on the documentation submitted and the scientific discussion within the Committee

the CHMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in Annex III for Priorix and associated names (see Annex I).