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ASSESSMENT REPORT

FOR

Rotarix

International Non-proprietary Name: human rotavirus, live attenuated

Procedure No. EMEA/H/C/639/X/0010

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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SCIENTIFIC DISCUSSION

INTRODUCTION

Rotarix is an oral vaccine. It contains one live attenuated strain (RIX4414) of human rotavirus. Rotarix is indicated for the active immunisation of infants from the age of 6 weeks for prevention of gastro-enteritis due to rotavirus infection. In clinical trials, efficacy was demonstrated against gastro-enteritis due to rotavirus of types G1P[8], G2P[4], G3P[8], G4P[8] and G9P[8].

The vaccination course consists of two doses. The first dose may be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. The vaccination course should preferably be given before 16 weeks of age, but must be completed by the age of 24 weeks.

Rotarix powder and solvent for oral suspension is already licensed for the above mentioned indication. To date, Rotarix powder and solvent for oral suspension has been approved in more than 100[A1] countries. In the European Union, the MAH submitted the initial application for Rotarix to the European Medicines Agency (EMEA) via the Centralised Procedure on 21 December 2004 and the EU Commission Decision was granted on 21 February 2006.

This application has been submitted under Article 8(3) of Directive 2001/83/EC as an extension to the licence for the Rotarix powder and solvent for oral suspension (EU/1/05/330/001-004) marketed by GlaxoSmithKline Biologicals to add the new pharmaceutical form oral suspension.

The rationale behind this submission is to follow the recommendations of international organisations such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO). The development of liquid vaccines is thought to lead to an easier handling for administration, lower costs in terms of shipment and storage, and a higher manufacturing capacity, all resulting in an enhancement of vaccine supply[amc2]. In addition, the application of Rotarix via tube and pre-filled oral applicator is thought to reduce the number of cases of maladministration that occurred with the lyophililised pharmaceutical form of Rotarix[A3].

The proposed pharmaceutical form oral suspension is intended for the same population for whom the Rotarix powder and solvent for oral suspension[A4] is currently licensed. Changes are proposed regarding method of administration due to the nature of the pharmaceutical form but not regarding dosing instructions.

QUALITY ASPECTS

Drug Substance

The manufacturing of the liquid formulation vaccine does not imply any change at the drug substance level. Nevertheless the MAH resubmitted the original drug substance data and included the alternative QC laboratories in a dedicated new building on the Wavre-Nord site and the latest stability data available for the HRV (human rotavirus) purified bulks. Results for three commercial purified bulks manufactured in 2002, after a storage period of 48 months, and results from the initial purified bulks stored for a maximum period of 73 months were provided. No loss of potency was observed.

Medicinal Product

Pharmaceutical Development

The active substance is unchanged as compared to the one included in the authorised HRV vaccine, Rotarix, presented as a lyophilised vaccine formulation. HRV liquid vaccine is an oral suspension, presented in monodose pre-filled oral applicator (glass) [amc5]or in polyethylene tubes. The liquid preparation is ready-to-use and is to be administered orally. The concentration of the active substance per nominal dose remains unchanged.

The liquid formulation only differs from the authorised lyophilised vaccine in its excipient composition, which is linked to manufacturing and vaccine stability constraints. HRV liquid vaccine is formulated to include as excipients sucrose, di-sodium adipate and DMEM (Dulbecco's Modified Eagle's Medium).

Manufacture of the Product

The liquid formulation is filled in monodose pre-filled oral applicators or in polyethylene tubes as outlined below:

- 1.75 ml clean, sterile oral applicator, uncoloured glass (Type I, Ph. Eur.) fitted with rubber tip caps. Plunger stoppers are of grey butyl rubber.
- 3 ml sterile polyethylene tubes provided with a nozzle finished by an opening, sealed by an extractable strip and protected by a cap in polypropylene.

The immediate packaging materials used for container-closure system of the liquid HRV vaccine are identical to those used for other vaccines manufactured by GlaxoSmithKline Biologicals[amc6].

The MAH described the filling process for both containers. The in-process controls during the formulation and the filling were presented.

Furthermore, detailed drawings for the polyethylene tube were provided, to allow a better understanding of the description of the polyethylene tubes.

The process validation was adequately detailed and assessed at the final bulk and finished product stages.

The procedures in place for the labelling, packaging operations and vaccine transportation were summarised and found acceptable.

Product Specification

The justification of specifications and a summary of the analytical methods were provided.

Stability of the Product

HRV liquid vaccine has been shown to be stable. There is no major potency loss upon storage at +2°C/+8°C. There is also no potency loss after incubation of the liquid HRV vaccine at 37°C for 7 days, although a decrease in virus titre is observed when it is incubated at 37°C for longer period of time. All the stability data presented have been generated on vaccine lots representative of the proposed commercial formulation and presentation. It is anticipated that the HRV liquid vaccine will remain stable up to 36 months at +2°C to +8°C. This is based on the comparability between the currently approved lyophilised presentation and the liquid presentation of HRV vaccine produced with a different formulation process, and based on the currently available data from real-time and accelerated stability studies.

The shelf-life at +2°C to +8°C does start from the date the vaccine is removed from the freezer for final labelling and packaging. Long-term stability studies have been undertaken in order to validate the storage of the liquid vaccine for 24 months at –20°C followed by 36 months at +2°C/+8°C.

The MAH agreed to provide an overview of the stability results after completion of all stability studies outlined under 3.2.P.8.2 in the documentation and to communicate the observation of any abnormal trend during the ongoing stability studies as outlined in the MAH Letter of Undertaking.

Discussion on chemical, pharmaceutical and biological aspects

The MAH submitted sufficient data to demonstrate that the quality of the liquid HRV vaccine is assured by a validated manufacturing process. The new specifications for the liquid formulation are adequately justified and the 20 first batches including commercial batches pass the specifications. On the basis of the available stability data, the liquid formulation is considered as a stable vaccine.

CLINICAL ASPECTS

Introduction

The clinical development plan was based on the MAH's proposal to recommend two doses of the liquid formulation of the HRV vaccine with the same virus strain (RIX4414) and identical viral strength (at least $10^{6.0}$ CCID50 as shown by live viral titration) administered according to the same vaccination schedule (two doses administered from the age of 6 weeks with an interval of at least four weeks between doses) as for the authorised lyophilised Rotarix vaccine.

In support of this line extension procedure, the immunogenicity and safety profile of the liquid formulation was reviewed and directly compared to data obtained with the authorised lyophilised Rotarix vaccine.

The immunogenicity, safety and reactogenicity data generated with the liquid formulation of Rotarix are derived from four studies (Rota-048, Rota-051, Rota-057 and Rota-061). The details of these studies are described in detail in the section on clinical efficacy below.

In all studies, a physical examination and recording of medical history established eligibility for enrolment. As blinding was technically not possible between the liquid and lyophilised formulation, the studies were open label for liquid formulation versus the lyophilised formulation. The placebo-controlled studies Rota-048 and Rota-051 were conducted in a double-blind manner for each HRV vaccine formulation and its respective placebo. Study Rota-061 was double-blind for three lots of the liquid formulation of GSK Bio HRV vaccine and Rota-057 was an open-label study.

In all trials, healthy infants previously uninfected with HRV were enrolled to receive two doses of the HRV vaccine. At first dose, infants were aged 6 to 12 weeks (Rota-048 and Rota-057), 6 to 10 weeks (Rota-051), and 10-17 weeks (Rota-061). The two HRV vaccine doses were to be given at the age of 2 and 3 months (Rota-048), 2 and 4 months (Rota-057), or 3 and 4 months (Rota-061). In study Rota-051, vaccine doses were to be given according to two WHO Expanded Program of Immunisation (EPI) vaccination schedules, i.e., 8 and 12 weeks or 8 and 16 weeks.

In study Rota-048, all routine childhood vaccines (i.e. Bacille Calmette-Guérin vaccine (BCG), diphtheria and tetanus with acellular pertussis vaccine (DTPa), *Haemophilus influenzae* type b (Hib) vaccine, hepatitis B vaccine (HBV) and inactivated polio vaccine (IPV), were administered at least 14 days apart from each dose of HRV vaccine or placebo. In study Rota-061, the first two doses of a combined childhood vaccine (DTPa-HBV-IPV/Hib) were co-administered at 3 and 4 months of age with each dose of HRV vaccine.

In study Rota-051, routine EPI vaccines (diphtheria-tetanus-whole cell pertussis [DTPw], HBV and oral polio vaccine [OPV]) were co-administered with the first and second dose of HRV vaccine. Similarly, in study Rota-057, combined DTPw-HBV/Hib vaccine as well as OPV, were administered concomitantly with the HRV vaccines.

In support of the extension application , the MAH also provided laboratory data collected on cases of gastro-enteritis (GE) episodes reported during the period between the administration of dose 1 and one to two months after administration of dose 2 of HRV vaccine or placebo. GE samples were tested for RV detection. RV - positive samples (RVGE) were subsequently analysed by Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) to determine the HRV strain (wild type or vaccine).

With regards to demographics, in studies Rota-048 and Rota-061, conducted in Finland, 98.7% and 98.6% of the subjects, respectively, were White-Caucasian. In study Rota-051, conducted in Vietnam, all subjects were Asian of south East Asian heritage. In study Rota-057, conducted in Panama, the majority of subjects (96.2%) was classified as 'other', reported as 'metisse or native chocoe'. With respect to other demographic characteristics, there were no major differences between the four studies. Within each study, the demographic profile of the vaccine groups and the placebo/control group was comparable with respect to mean age, gender, mean height and mean weight.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Due to the nature and mechanism of action for vaccines evaluation of pharmacokinetic properties is not required for the Marketing Authorisation and was not considered necessary for this extension application.

Pharmacodynamics

[A7]Mechanism of action

The immunologic mechanism by which Rotarix protects against rotavirus gastro-enteritis (GE) is not completely understood. A relationship between antibody responses to rotavirus vaccination and protection against rotavirus GE has not been established (see also section 5.1 of the SPC). Comparative immunogenicity data (seroconversion rate, serum anti-rotavirus IgA antibody titres and HRV shedding) are discussed under section "clinical efficacy" below.

Clinical efficacy

The clinical efficacy was supported by four studies, which are described below:

Study Rota-048 (Finland)
Design: Phase II, double-blind, randomised, placebo controlled study with 4 parallel groups. Subjects received 2 doses of either liquid or lyophilised formulation of HRV vaccine, or the respective placebo formulation, according to a 0, 1 month schedule given to healthy infants previously uninfected with HRV and aged 2 months (6 to 12 weeks) at the time of first vaccination:

- Group HRV liquid formulation (N = 100)
- Group Placebo for HRV liquid formulation (N = 25)
- Group HRV lyophilised formulation (N = 100)
- Group Placebo for HRV lyophilised formulation (N = 25)

All subjects received routine childhood vaccinations as described above. Routine vaccines were to be administered at least 14 days apart from each dose of the HRV vaccine/ placebo.

Objectives:
The primary objective was to assess immunogenicity of the liquid formulation of the HRV vaccine compared to the lyophilised formulation of the HRV vaccine.
Secondary objectives were to assess the immunogenicity in terms of geometric mean antibody concentration (GMC) after each dose and seroconversion rates after each dose and on combined doses; and to assess the reactogenicity and safety of the liquid formulation of the HRV vaccine compared to the lyophilised formulation of the HRV vaccine.

Results:
250 infants aged 9.1 ± 1.94 weeks (mean ± SD) were enrolled and vaccinated.
The immunogenicity (in the according-to-Protocol (ATP) cohort) in terms of vaccine take on combined doses, anti-rotavirus IgA seroconversion rates and rotavirus shedding was similar between the two vaccine formulations. The seroconversion rates at one month after the second dose were 83.7% for the lyophilised formulation and 90.0% for the liquid formulation. GMCs calculated on all subjects were 360.6 U/ml after lyophilised HRV vaccine and 301.3 U/ml after liquid formulation HRV vaccine. Vaccine take on combined dose 1 and dose 2 was 93.4% with the liquid formulation and 89.4% with the lyophilised HRV vaccine formulation, and was not statistically different between the two vaccine formulation groups. No rotavirus shedding and anti-rotavirus IgA seroconversion was observed in the placebo groups.

<u>Rota-051 (Vietnam)</u>
Design: Phase II, double-blind, randomised, placebo controlled study with 3 parallel groups in healthy infants previously uninfected with HRV and aged 6 to 10 weeks at the time of first vaccination with liquid formulation of HRV vaccine. Subjects received a second dose of liquid HRV vaccine either one month post dose 1 (+ placebo at two months post dose 1) or at two months post dose 1 (+ placebo one month post dose 1), or received 3 doses of placebo.

- Group HRV liquid formulation 0, 1 month (N = 150), i.e. co-administered with first and second dose of EPI vaccines referred to as V–V–PL group
- Group HRV liquid formulation 0, 2 months (N = 147), i.e. co-administered with first and third dose of EPI vaccines, referred to as V–PL-V group
- Group Placebo for HRV lyophilised formulation (N = 78)

Routine EPI childhood vaccines (DTPw, HBV and OPV), were co-administered with each dose of HRV vaccine or placebo[amc8].

Objectives:
The primary objective was to assess the immunogenicity of HRV liquid vaccine versus placebo, in terms of anti-RV IgA antibody seroconversion at month 2, when administered concomitantly with the first and second routine EPI vaccines.
Secondary objectives were to assess immunogenicity of HRV liquid vaccine versus placebo, in terms of anti-RV IgA antibody seroconversion at month 2 when administered concomitantly with the first and second doses of routine EPI vaccines, and at month 3, when co-administered with the first and third doses of routine EPI vaccines. The immunogenicity in terms of GMC after two HRV vaccine doses and the reactogenicity and safety of the liquid formulation of the HRV vaccine versus placebo as well as the presence of RV in GE stools collected after administration of first dose up to month 3 were also assessed as secondary objectives.

Results:
375 infants aged 8.7 ± 1.07 weeks (mean ± SD) were enrolled and vaccinated.
The anti-RV seroconversion rates measured one month after dose 2 of the HRV vaccine were 63.3% (95% CI: 54.3;71.6) when co-administered with the first and second dose of EPI vaccines (V-V-PL) and 81.5% (95% CI: 73.4;88.0) when co-administered with the first and third dose of routine EPI vaccines (V-PL-V). At one month after dose 2 of HRV vaccine, anti-RV GMCs calculated on all

subjects were 77.4 U/ml (95% CI: 55.2; 108.6) in the V-V-PL group and 176.3 U/ml (95% CI: 123.8; 251.1) in the V-PL-V group. The seroconversion rate observed in the placebo group was 7.8% when the mean age of the subjects was 17.3 weeks indicating that natural infection with wild type RV occurred rather early in these subjects during the study. Nonetheless, the seroconversion rate in the placebo group was significantly lower than the rates observed in both HRV vaccine groups.
RV was not isolated from any of the stool samples tested in case of GE episodes from dose 1 up to visit 4.

Rota-057 (Panama)
This was a Phase III, open-label, randomised (1:1) study with two parallel groups receiving two different formulations of HRV vaccine, either liquid (HRV_LIQ) or lyophilised formulation (HRV_LYO), according to a two-dose 0, 2 month vaccination schedule given to healthy infants previously uninfected with HRV and aged 2 months (6 to 12 weeks) at the time of first vaccination.
Routine EPI vaccines (i.e. combined DTPw-HBV/Hib vaccine) including OPV, were administered concurrently with the HRV vaccines, and according to the EPI recommendations in Panama.

Objectives:
The primary objective was to assess the immunogenicity, in terms of anti-rotavirus IgA antibody seroconversion rates at one month after the two-dose primary vaccination course with the liquid formulation of the HRV vaccine compared to that of the registered lyophilised HRV vaccine.
Secondary objectives were to assess the immunogenicity of the two formulations of HRV vaccine, after a two-dose primary vaccination course in terms of GMC and in terms of vaccine take (in a subset of subjects). The reactogenicity and safety of the study vaccines was also assessed.

Results:
1274 infants aged 8.6 ± 0.86 weeks (mean ± SD) were enrolled and vaccinated.
From the total vaccinated cohort of 1274 subjects (636 subjects in the Rotarix liquid formulation group: HRV_LIQ and 638 subjects in the Rotarix lyophilised formulation group: HRV_LYO), 374 subjects were eliminated.

A total of 900 subjects (456 in the HRV_LIQ group and 444 in the HRV_LYO group) were included in the ATP cohort for immunogenicity. The code ‘essential serological data missing’ was the main cause of elimination (37% of the eliminated subjects: 139 out of 374[amc9])..Other reasons are presented below:

- 83 subjects received a vaccine dose that was not administered according to protocol.
- 2 subjects were initially seropositive or had an unknown status for serum anti-rotavirus IgA antibodies on the day of dose 1.
- 50 subjects were not compliant with vaccination schedule (including wrong and unknown dates).
- 20 subjects received concomitant vaccines forbidden in the protocol (such as Rotarix given during the National EPI program, or other vaccines (Prevenar and BCG during the period within 14 days before and after each dose of study vaccine).

[A10]
Among the causes, for 38 (27%) of the 139 subjects eliminated due to missing essential serological data “irrelevant results” were obtained. The MAH clarified the root cause of these irrelevant results and the distribution of these subjects in the two HRV vaccine groups, as these were mainly protocol deviations and unavailable or invalid laboratory results which were evenly distributed between the HRV_LIQ and HRV_LYO groups.

In total, of the 1274 subjects included in the Total Vaccinated Cohort (TVC), 165 subjects were excluded from the ATP cohort for safety due to: concomitant vaccination forbidden in the protocol (20 subjects), vaccine dose not administered as defined in the protocol (83 subjects), initially positive result for RV (in serum or in stool) / unknown status for RV on day of dose 1 (62 subjects).
1109 subjects (557 subjects in the HRV_ LIQ group and 552 subjects in the HRV_ LYO group) were included in the ATP cohort for safety.

Of the 1109 subjects included in the ATP cohort for safety, 209 subjects were excluded from the ATP cohort for immunogenicity due to protocol violation related to inclusion/exclusion criteria in the study (3 subjects), medication forbidden in the protocol (3 subjects), non-compliance with vaccination schedule (50 subjects), non-compliance with blood sampling schedule (14 subjects), post-vaccination serological data and planned stool data not available (139 subjects[amc11]).

Seroconversion rates following two doses of liquid formulation HRV vaccine co-administered with OPV were 80.8% (95% CI, 76.9; 84.4) with a GMC calculated on all subjects of 151.2 U/ml (95% CI: 128.0; 178.7). The seroconversion rate in the group that received the lyophilised formulation was 73.5% [95% CI: 69.1%; 77.6%] with a GMC of 111.7 U/ml [95% CI: 93.5%; 133.4]. When considering GMCs calculated on seropositive subjects, the GMCs after the liquid formulation and after the lyophilised HRV vaccine were found to be comparable (287.8 U/ml [95% CI: 250.2; 331.2] and 266.6 U/ml [95% CI: 228.6; 310.8], respectively). In terms of vaccine take, no difference was detected between the two HRV groups.

Rota-061 (Finland)
This phase III, double-blind, randomised, study with 4 parallel groups was carried out in healthy infants previously uninfected with HRV and aged 3 months (10 to 17 weeks) at the time of first vaccination. Subjects received 2 doses of one of the three clinical lots of liquid formulation of HRV vaccine or received 2 doses of the registered lyophilised HRV vaccine, according to a 0, 1 month schedule:

- Group HRV liquid formulation lot A (“Liq_A”, N = 298)
- Group HRV liquid formulation lot B (“Liq_B”, N = 302)
- Group HRV liquid formulation lot C (“Liq_C”, N = 300)
- Group HRV lyophilised formulation (“Lyo”, N = 300)

The combined childhood vaccine DTPa-HBV-IPV/Hib (Infanrix hexa) was administered concomitantly with each dose of the HRV vaccine.

Objectives:
The co-primary objectives were
1) to demonstrate the lot-to-lot consistency of the liquid formulation of the HRV vaccine in terms of immunogenicity as measured by serum anti-rotavirus IgA antibody levels one month after dose 2 and
2) to demonstrate non-inferiority of the liquid formulation to that of lyophilised formulation of the HRV vaccine in terms of seroconversion rates one month after dose 2.
Secondary objectives were to demonstrate non-inferiority of the liquid formulation to that of lyophilised formulation of the HRV vaccine in terms of serum anti-rotavirus IgA antibody levels one month after dose 2. The lot-to-lot consistency of the liquid formulation of the HRV vaccine was also assessed in terms of reactogenicity. The safety of the study vaccines was also evaluated.

Results
1200 infants aged 11.6 ± 1.25 weeks (mean ± SD) were enrolled and vaccinated.
Consistency of the three HRV vaccine lots of the liquid formulation was demonstrated since, for all pairs of lots, the two-sided 95% CIs for the ratio of anti-rotavirus IgA antibody GMCs one month after dose 2 were within the [0.5; 2] clinical limit interval.
Non-inferiority, in terms of seroconversion rates, of the liquid formulation to that of lyophilised formulation of the HRV vaccine was demonstrated.
Non-inferiority, in terms of serum anti-rotavirus IgA antibody levels, of the liquid formulation to that of lyophilised formulation of the HRV vaccine was demonstrated since the upper limit of the two-sided 95% CI for the ratio of anti-rotavirus IgA antibody GMCs one month after dose 2 between the lyophilised formulation of HRV vaccine and (over) the liquid formulation of HRV vaccine was less than or equal to 2.

Incidence of GE between dose 1 and 1 to 2 months post dose 2
In studies Rota-048 and Rota-051, the incidence of GE between dose 1 and 1 to 2 months post dose 2 was similar between the groups receiving HRV (lyophilised or liquid) and placebo. In study Rota-048,

the reported incidence of GE was 11.0% (95%CI: 5.6%; 18.8%) for the HRV lyophilised (HRV_LYO), 6.0% (95%CI 2.2%; 12.6%) for the HRV liquid (HRV_LIQ), and 12% (95%CI: 4.5%; 24.3%) for the placebo group. In Rota-051, the percentages were 16.7% (95% CI: 11.1%; 26.6%) and 15.6% (95% CI: 10.2%; 22.5%) for the two groups receiving HRV_LIQ and 15.4% (95% CI: 8.2%; 25.3%) for the placebo group.

A total of 13 RVGE cases (6 from HRV_ LYO, 7 from HRV_LIQ) were reported across the 4 studies, among 2971 recipients of the HRV vaccine (1933 received the liquid formulation, 1038 received the lyophilised formulation) and 128 placebo recipients. Out of these 13 cases, 8 were positive for the HRV vaccine strain (6 from HRV_LIQ and 2 from HRV_LYO). None of these cases was reported as serious adverse event nor resulted in hospitalisation. These data indicate that there is no difference in terms of RVGE incidence between the HRV liquid and the approved HRV lyophilised formulations during the period within the administration dose 1 and one to two months post dose 2. This observation was expected as the immunogenicity and reactogenicity profiles as well as the shedding rate after vaccination are similar between both formulations[amc12].
Of note, the efficacy against RVGE between dose 1 and 14 days post dose 2 has been evaluated in a large controlled, randomised (1:1 vaccine to placebo), double blind efficacy study, Rota-036, with the lyophilised formulation. This study demonstrated that during the period from dose 1 to14 days post dose 2 (mean duration: 2.4 months in each study group), significantly fewer subjects in the HRV vaccine group reported RVGE caused by the circulating wild-type RV compared to the placebo group (P-value = 0.004). The corresponding vaccine efficacy against any RVGE within that period was 87.3% (95%CI: 36.2%; 98.7%).

Discussion on clinical efficacy
The submitted data provided enough indication that the immunogenicity (in terms of IgA antibody seroconversion rates, GMC and vaccine take) of this new liquid formulation is similar to the already registered lyophilised formulation.

The CHMP noted that in study 051 the 0, 1 month administration schedule with the liquid formulation resulted in significantly lower seroconversion rates and GMCs compared to the 0, 2 month schedule with the liquid formulation.

In this study seroconversion rate and GMCs were also significantly lower in the V-V-PL group than in the V-PL-V group (and than historical controls with the lyophilised formulation (Rota-006 seroconversion 86.5%, GMCs 197.2 in 787 subjects)). In fact, the seroconversion rate was only 63% and GMCs were 77.4 U/ml post-dose 2 in the group that received Rotarix at 8 and 12 weeks in combination with other EPI vaccines. The MAH clarified the reason for the poor outcome of this study and presented implications on the recommended dosing interval for Rotarix in countries where the EPI schedule is used.

The immaturity of the immune system and the higher level of maternal antibodies in younger infants have been reported previously as a cause of poor immune response following vaccination with the HRV vaccine (*Ruiz Palacios et al* 2002). In other studies (Rota-004, Rota-008 and Rota-014), it was observed that higher levels of transplacentally transmitted maternal antibodies at younger age tend to decrease the level of immune response to HRV. These elements account for most of the difference in vaccine response observed between the V-V-PL (8-12 weeks) group and the V-PL-V (8-16 weeks) group.

However, the benefit of vaccinating at an older age should be balanced with the fact that natural RV infections can occur at an early age as shown in the placebo group of study Rota-051, where seroconversion rates in the placebo group were 7.8% at a mean age of 13.0 weeks (age at dose 2) and 15.4% at a mean age of 17.3 weeks (age at dose 3). Besides the observed difference in seroconversion between the two schedules in this study conducted in Vietnam, the overall rate of seroconversion tends to be lower than the seroconversion levels generally observed in developed countries. In addition, the co-administration of HRV with OPV has been shown to result in slightly, although not significantly, decreased seroconversion rates. These events have been observed in other studies conducted in other developing countries

The CHMP further noted that in the phase III trial 057, the number of subjects with available results was comparably low. The detailed analysis of the reasons for elimination from the ATP immunogenicity cohort indicated that these were mainly protocol deviations and unavailable or invalid laboratory results. The number of excluded subjects was evenly distributed between the "HRV_LIQ" and "HRV_LYO" groups, indicating that the results are not biased by a difference in the distribution of excluded subjects.

Therefore, the conclusions of the study seem not to be affected by the relatively high rate of excluded subjects: Rota-057 showed no statistical differences in terms of immunogenicity and reactogenicity and safety between lyophilised and liquid formulations. Similar conclusions can be drawn from studies Rota-048 (N= 250) and Rota-061 (N= 1200), that also compared the two formulations, further confirming the results of Rota-057. The CHMP considered that in general, a drop-out rate above 20% raises doubt on the quality of the results, however acknowledged that no obvious bias could be detected and no differences between both treatment groups could be detected.

Concerning RV GE episodes, no difference between the lyophilised and the liquid formulation could be detected in all four studies.

To evaluate effectiveness of the new formulation after approval, the MAH committed to co-operate with Public Health bodies to monitor effectiveness before and after switching from the approved to the new formulation as outlined in the Letter of Undertaking (see Annex VI to this report). The MAH committed to carry out an observational, prospective, sentinel hospital-based multicentre surveillance study (case-control design) in Belgium to monitor actively the incidence and proportion of hospitalisations for laboratory-confirmed cases of RV GE in children < 5 years of age.

Given the high rotavirus vaccination coverage once Rotarix is introduced in an universal mass vaccination setting such as in Belgium, the expected rapid uptake of Rotarix liquid formulation, once introduced, and the high expected clinical efficacy of rotavirus vaccines, the MAH stated that it will not be possible to effectively and rapidly generate vaccine effectiveness data with specific point estimates (using the case control study design, the screening method or alternative designs) due to the lack off cases observed. For this reason the MAH proposed a staggered two-step approach with close monitoring of disease trends (sentinel surveillance), followed by an epidemiological investigation and effectiveness evaluation, in the event of increasing disease trends.

Results of the study in Belgium are expected to be relevant for other European countries considering the introduction of Rotarix, liquid and/or lyophilised formulations, within their routine childhood immunisation schedule.

Clinical safety

Patient exposure

The MAH presented safety and reactogenicity data collected from 1933 infants who had received Rotarix liquid formulation through 4 clinical studies (Rota-048, 051, 057 and 061).

- Study **Rota-048**, conducted in Finland, was a phase II, double-blind, randomised, placebo controlled study to compare the immunogenicity, reactogenicity and safety of the liquid formulation of the HRV vaccine to the lyophilised formulation of the HRV vaccine given as a two-dose primary vaccination in healthy infants at the age of 2 and 3 months. A total of 250 infants aged 6 to 12 weeks were enrolled to receive two doses of HRV vaccine, either liquid or lyophilised formulation, or the respective placebo formulation. Of these, 240 infants were included in the Cohort for safety. Routine childhood vaccines, i.e. Bacille Calmette-Guérin vaccine (BCG), diphtheria and tetanus with acellular pertussis vaccine (DTPa), *Haemophilus influenzae type b* (Hib) vaccine, hepatitis B vaccine (HBV) and inactivated polio vaccine (IPV), were administered at least 14 days apart from each dose of HRV vaccine or placebo. The reactogenicity and safety of the HRV vaccines were assessed as secondary objective.

- Study **Rota-051**, conducted in Vietnam, evaluated the immunogenicity and reactogenicity/safety of the liquid formulation of the HRV vaccine when administered with the first and second routine EPI immunisations (DTPw, HBV and OPV), i.e. at 6-10 weeks of age and one month later (schedule 0, 4 weeks); or when administered concomitantly with the first and third doses of routine EPI vaccines, i.e. at 6-10 weeks of age and 2 months later (schedule 0, 8 weeks). A total of 375 infants aged 6 to 10 weeks were enrolled to receive two doses of the liquid formulation of the HRV vaccine (+ 1 dose of placebo) or three doses of placebo. Of these, 352 infants were included in the cohort for safety. The safety and reactogenicity of the liquid HRV vaccine versus placebo was assessed as secondary objective.

- Study **Rota-057**, conducted in Panama, compared the immunogenicity of the liquid formulation of the HRV vaccine to the lyophilised formulation of the HRV vaccine, when administered concurrently with routine EPI vaccinations, including OPV. A total of 1274 healthy infants aged 6 to 12 weeks were enrolled to receive two doses of HRV vaccine, either liquid or lyophilised formulation, at the age of 2 and 4 months. Of these, 1109 infants were included in the cohort for safety. The reactogenicity and safety of the HRV vaccines were assessed as secondary objective.

- Study **Rota-061**, conducted in Finland, evaluated the clinical consistency in terms of immunogenicity and reactogenicity of three production lots of the liquid formulation of the HRV vaccine and also evaluated the liquid formulation as compared to the lyophilised formulation of the HRV vaccine in terms of immunogenicity, reactogenicity and safety. A total of 1200 infants aged 10 to 17 weeks were enrolled to receive two doses of HRV vaccine according to a 3, 4 months schedule, administered concomitantly with routine childhood vaccination (DTPa-HBV-IPV/Hib). Of these, 1115 infants were included in the cohort for safety. The lot-to-lot consistency in terms of reactogenicity of the liquid formulation of the HRV vaccine as well as the safety of both HRV vaccine formulations were assessed as secondary objectives.

Adverse events

Solicited symptoms
Irritability was the most frequently reported solicited symptom in studies Rota-048, Rota-057 and Rota-061, whereas fever was the most frequently reported solicited symptom in study Rota-051. The incidence of irritability considered as related to vaccination by the investigator was comparable across the different study groups (35.4%-47.7% in Rota-048, 23.1%-25.2% in Rota-057 and 64.0%-73.0% in Rota-061). For study Rota-051 conducted in Vietnam, a lower incidence of irritability was observed in all study groups (37.1%-39.4%) when compared to the incidences in studies Rota-048 (63.3%-67.5%) and Rota-061 (65.5%-74.5%) conducted in Finland. In study Rota-057 conducted in Panama the irritability incidence was intermediate (50.2%-52.6%). Ethno-cultural differences may account for these variable incidences of irritability.

Similarly, the incidence of fever considered as related to vaccination ranged from 20.1% to 22.2 % in Rota-051, 23.1% to 25.0% in Rota-057 and 22.2% to 24.3% in Rota-061, and also was comparable between the study groups. Since no concomitant vaccines were administered in trial Rota-048, the lowest incidence of fever was observed in this trial (4.1%). As expected, higher incidence for fever was seen in subjects who had received DTP-based routine concomitant vaccine administrations (Rota-051, Rota-057, Rota-061).

Overall, there was no increase in incidence of solicited symptoms with subsequent doses of HRV vaccine (both formulations).

Unsolicited symptoms
One difference between the liquid and the lyophilised formulation was noted: Unsolicited symptoms of grade 3 intensity seem to have occurred more frequently in the liquid formulation group (6.3% vs. 3%, p=0.036).

Serious adverse events and deaths

No fatal outcomes were reported following vaccination with liquid or lyophilised HRV vaccine in the submitted clinical studies.
In total, 63 subjects (3.26%) reported at least one SAE following vaccination with liquid HRV vaccine and 45 subjects (4.34%) reported at least one SAE following vaccination with lyophilised HRV vaccine.

In total, one SAE case, reported in study Rota-051, was assessed as at least possibly related to vaccination by the investigator: in the 8, 12 weeks group, a 9-week-old girl reported one SAE (preferred term abdominal pain, Case ID B0437934A) one day after the dose 1 of liquid HRV vaccine and was hospitalised. The event was considered to be causally related to vaccination by the investigator. The subject recovered and the event resolved without sequelae.

Data on SAEs from dose 1 of HRV vaccine up to the end of the extended safety follow-up from Rota-061 was also provided.
The extended safety follow-up phase included the period starting from the day after visit 3 (at month 2) up to the contact at month 7 (i.e. up to six months after the last dose of the HRV vaccine).

During the extended safety follow-up phase, a total of 18 subjects (3 subjects in the Liq_A group, 2 subjects in the Liq_B group, 11 subjects in the Liq_C group and 2 subjects in the Lyo group) reported at least one SAE. Most of the SAEs reported during the extended safety follow-up phase (n = 13) were under the SOC 'Infections and infestations' and there were 3 SAEs reported under the SOC of 'Nervous system disorders'. All the SAEs had resolved.

During the entire study period, a total of 36 subjects reported at least one SAE of whom 18 subjects reported SAEs during the extended safety follow-up phase. None of the SAEs were causally related to vaccination. No fatal events were reported during the study.

Intussusception (IS)

There were no reports of IS cases in the four studies with Rotarix liquid formulation, included in this submission.

Discontinuation due to adverse events

Of a total of 3099 subjects enrolled and vaccinated, 135 subjects failed to complete the trials. The majority of subjects (97.0%) dropped out for reasons not associated with an adverse event. The most common reasons for withdrawal were: lost to follow-up (63/135; 46.7%), consent withdrawal for reasons other than an adverse event (48/135; 35.6%); and migration from the study area (19/135; 14.1%).

Four subjects were withdrawn from the study after vaccination with HRV vaccine due to SAE (3 subjects) or non-serious AE (one subject):

- In study Rota-048, one subject (no. 522) dropped out from the study due to non-serious abnormal tonus (hypertonus) 32 days after dose 1 of the lyophilised HRV vaccine. The investigator considered that this adverse event was not causally related to vaccination.
- In study Rota-051, one subject (no. 465) in the V-PL-V group experienced pneumonia 27 days after dose 1 of the liquid HRV vaccine and was hospitalised. The parents/guardians of the subject withdrew their child at visit 2. This SAE was not considered to be causally related to vaccination.
- In study Rota-057, one subject (no. 1661) in the lyophilised HRV vaccine group was withdrawn from the study due to a SAE of pneumonia. This medical condition developed 69 days after dose 2, lasted for 12 days and the subject recovered. The investigator considered that there was no reasonable possibility that the pneumonia may have been caused by the HRV vaccine.
- In study Rota-061, one subject (no. 426) in the lyophilised HRV vaccine group was withdrawn from the study due to a SAE (Infantile spasms) with onset 2 days after dose 2. This SAE was not considered to be causally related to vaccination.

Post marketing experience

No post-marketing data were available for the liquid formulation of Rotarix when this file was submitted in October 2007[amc13].

Maladministration (injection[amc14]*)*
In the frame of the extension procedure it was considered relevant to provide background information on cases of maladministration reported for the existing formulation of Rotarix as described below. The new pharmaceutical form is thought to reduce maladministrations due to easier handling.
In the 4th periodic safety update report (PSUR, period covered: 12 January 2007 –11 July 2007) for Rotarix, since launch up a total of 120 cases of incorrect route of administration (e.g. injection) of the Rotarix lyophilised formulation have been reported to the MAH. Of these 120 cases, 27 cases were associated with non-serious adverse events and 3 were associated with serious adverse events. For the 3 serious cases, the events resolved.

A large increase of reports was reported in Spain, where the vaccine is administered by nurses and frequently by non-paediatric personnel. The MAH has agreed to implement several measures to reinforce the information about the correct route of administration of Rotarix since an increasing number of such reports was noted in the period of the previous PSUR. In the first place, all paediatricians in countries where Rotarix was available were reminded of the appropriate route of administration of Rotarix through an "information letter" and other means.

The MAH has developed an action plan to increase the communication and education of the relevant personnel and to minimise the risk of incorrect route of administration in Spain. The action plan was submitted to the EMEA on March 11th 2008 and is being implemented in Spain as from March 2008.

[A15]From a global perspective, the number of maladministration cases per 100.000 doses administered in the EU/EEA has decreased from 18/100.000 before the 4th quarter of 2007, to less than 2/100.000 during the 4th quarter of 2007.

Additional efforts were also made through changes to the label, pack and leaflet to further emphasise the oral administration route and consequently reduce the risks of maladministration (variation II-005). Since these vaccines are currently being introduced into the markets, it is considered premature to evaluate the impact of this change by the reporting rates observed in the 5th PSUR (period covered 12 July 2007 11 January 2008). The MAH is monitoring for any reports that would follow one of these newly labelled and packaged vaccines by controlling the lot numbers.

Discussion on clinical safety

The available data indicate that the safety of this new formulation is not different compared to that of the already registered formulation. The CHMP highlighted that 1933 patients is not a very large database.

The CHMP considered that this population size is not sufficient to detect a potential increase in intussusception (IS) associated with the liquid formulation. However, it was agreed with the MAH that considering that the same viral strain at the same potency and the same vaccination schedule will be used for both formulations there is no reason to believe that the risk with respect to IS would differ between the two formulations. Thus, the MAH's proposal to follow the incidence of IS via Post Marketing Surveillance was considered adequate.

Unsolicited symptoms of grade 3 intensity seem to have occurred more frequently in subjects that received the liquid formulation in the pooled data from the studies (6.3% vs. 3%, p=0.036). Because of multiplicity issues these data should however be considered with caution. Concerning solicited symptoms no clinically significant differences could be detected between the liquid and lyophilised formulation[amc16].

Concerning maladministration, the CHMP considered that continued attention of the MAH to this issue is most certainly warranted[amc17]. The CHMP however highlighted that the number of maladministration cases per 100.000 doses administered in the EU/EEA has decreased from 18/100.000 before the 4th quarter of 2007, to less than 2/100.000 during the 4th quarter of 2007. [A18]No further steps are considered necessary for the time being.

Based on the fact that this new formulation contains the same virus strain, identical strength and is administered according to the same vaccination schedule, it can be assumed that the safety profile will not be different to that of the oral suspension.

PHARMACOVIGILANCE

Detailed description of the Pharmacovigilance system

The MAH has provided documents that set out a detailed description of the system of Pharmacovigilance. A statement, indicating that the MAH has the services of a qualified person responsible for Pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan

The MAH submitted an updated risk management plan.

The MAH has updated the risk management plan with data specific for the liquid and the lyophilised formulation (Version 004).

Table 1: Summary of the EU Risk Management Plan for Rotarix

Safety concerns	Qualification	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Actions
Bronchitis	Potential risk	Study Rota 036	None
IS	Potential risk	Active surveillance in EU: a/ Germany (ESPED) b/ UK (BPSU): on hold Observed versus expected analysis PASS study in Mexico	SPC: 4.3. Contraindications: Previous history of intussusception. Subjects with uncorrected congenital malformation of the gastrointestinal tract that would predispose for intussusception. 4.8. Undesirable Effects: The risk of intussusception has been evaluated in a large safety trial conducted in Latin America and Finland where 63225 subjects were enrolled. This trial gave evidence of no increased risk of intussusception in the Rotarix group when compared with the placebo group.
Pneumonia deaths	Potential risk	PASS study in Mexico	None
Vaccine effective-ness	Missing information	Study in Belgium	SPC: 4.4. Special warnings and precautions for use: A protective immune response may not be

Safety concerns	Qualification	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Actions
			elicited in all vaccinees (see section 5.1).
Monitoring the diversity of circulating RV strains in a post-marketing setting	Missing information	European Rotavirus Surveillance Network	
Genetic stability of vaccine virus	Missing information	Study Genetic Stability of Vaccine Virus in Belgium	None
Vaccine virus transmission	Missing information	Study Rota 052	SPC: 4.4. Special warnings and precautions for use: Cases of transmission of this excreted vaccine virus to seronegative contacts of vaccinees have been observed without causing any clinical symptom.
Use in preterm infants	Missing information	Study Rota 054	SPC: 4.4. Special warnings and precautions for use: Limited data in 140 premature children indicate that Rotarix can be given to premature children, however a lower immune response may be observed and the level of clinical protection remains unknown.
Use in immunocompromised infants	Missing information	Study Rota 022	SPC: 4.3.Contraindications: Infants who have known or suspected immunodeficiency. Asymptomatic HIV infection is not expected to affect the safety or efficacy of Rotarix. However, in the absence of sufficient data, administration of Rotarix to asymptomatic HIV subjects is not recommended. 4.4. Special warnings and precautions for use: Rotarix should be administered with caution to individuals with immunodeficient close contacts, such as individuals with malignancies, or who are otherwise immunocompromised or individuals receiving immunosuppressive therapy.
Potential for medical errors	Specific EU requirement	Review in PSUR The reporting frequency of the cases of maladministration will be closely monitored by country to evaluate the impact of the changes to the label and packaging. Results of this activity will be summarised in futures PSURs.	SPC: 4.4. Special warnings and precautions for use: Rotarix should under no circumstances be injected. Newly labelled and packaged vaccines became available.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

OVERALL CONCLUSIONS, RISK/BENEFIT ASSESSMENT AND RECOMMENDATION

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

The CHMP considered that no additional non-clinical studies were required, as the studies assessed for the granting of the Marketing Authorisation for Rotarix were considered sufficient.

Pharmacokinetics

Due to the nature and mechanism of action for vaccines evaluation of pharmacokinetic properties is in general not required for the Marketing Authorisation and was thus not requested by the CHMP.

Efficacy

The CHMP agreed that the submitted data provided sufficient evidence that the immunogenicity (in terms of IgA antibody seroconversion rates, GMC and vaccine take) of the new liquid formulation is similar to the already registered lyophilised formulation.

Additionally, to evaluate effectiveness of the new formulation after approval, the MAH committed to co-operate with Public Health bodies to monitor effectiveness before and after switching from the approved to the new formulation as outlined in the Letter of Undertaking. The CHMP considered that this measure would be appropriate to follow up the efficacy of the liquid formulation in the clinical setting.

Safety

From the safety data of the studies submitted in support of this line extension the CHMP concluded that Rotarix was found to be generally safe and well-tolerated in the target population, with a safety profile which is consistent with that of the marketed Rotarix lyophilised formulation. Therefore, the contraindications, warnings and precautions contained in the PI of the already approved Rotarix lyophilised formulation are applicable to the new formulation.

The CHMP therefore concluded that the introduction of the liquid formulation did not significantly alter the safety profile of the combination product.
From the safety database all the adverse reactions reported in clinical trials (lyophilised and liquid formulation) and post-marketing (lyophilised formulation) have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in the Risk Management Plan (RMP) adequately addressed these.

User consultation

The proposed Package Leaflet for Rotarix liquid formulation provides exactly the same information to the patient than the approved Package Leaflet for Rotarix lyophilised formulation except for section 6 since the composition and containers are different.

During the approval process for Rotarix, user consultation was undertaken for the Package Leaflet. Therefore, as the MAH provided justification for not performing a user testing consultation, the CHMP considered user testing not necessary to support this line extension.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Routine pharmacovigilance was adequate to monitor the safety of the product.

- No additional risk minimisation activities were required beyond those included in the Product Information.

The submitted data provided sufficient justification that the immunogenicity (in terms of IgA antibody seroconversion rates, GMC and vaccine take) of this new liquid formulation can be considered similar to the already registered lyophilised formulation.

The SPC is similar to the already registered lyophilised formulation. The section on the instructions for administration of the vaccine has been considerably improved in order to avoid injection of the oral suspension. The form of the tube no longer resembles a syringe.

The available data indicate that the safety of this new formulation is not different than that of the already registered formulation. The CHMP noted that the safety database is limited (1933 pts). However, based on the fact that this new formulation contains the same virus strain, identical strength and is administered according to the same vaccination schedule as the lyophilised formulation[A19], there is no reason to believe that its safety profile will be different. The fact that the immunogenicity [A20]is similar in the conducted clinical trials is also an indication that this new formulation has a similar effect in the body than the already registered one.

Additionally, to evaluate effectiveness of the new formulation after approval, the MAH committed to co-operate with Public Health bodies to monitor effectiveness before and after switching from the approved to the new formulation in a surveillance study as outlined in the Letter of Undertaking.

Taken together, the efficacy and safety results from the clinical data submitted in support of this line extension did not indicate any significant difference between the existing pharmaceutical form (powder and solvent for oral suspension) and the new pharmaceutical form (oral suspension). The CHMP therefore considered that the benefit/risk [A21]of Rotarix oral suspension is favourable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Rotarix oral suspension in the indication “active immunisation of infants from the age of 6 weeks for prevention of gastro-enteritis due to rotavirus infection” was favourable and therefore recommended the granting of the marketing authorisation.