EMADOC-1700519818-1955530
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMA/VR/0000256456

Invented name: Pradaxa

International non-proprietary name: Dabigatran etexilate

Note

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

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The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to PRAC/CHMP members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission deadline	21 March 2025	27 February 2025	☐
☐	Validation	7 April 2025	3 March 2025	☐
☐	Start date	8 April 2025	8 April 2025	☐
☐	PRAC Rapporteur AR	19 May 2025	12 May 2025	☐
☐	PRAC comments	23 May 2025	n/a	☐
☐	CHMP comments	26 May 2025	n/a	☐
☐	Updated PRAC Rapporteur AR	27 May 2025	n/a	☐
☐	Start of CHMP written procedure	3 June 2025	3 June 2025	☐
☐	PRAC outcome	3 June 2025	3 June 2025	☐
☐	CHMP Outcome/Request for Supplementary Information	5 June 2025	5 June 2025	☐
☐	Re-start date	8 July 2025	8 July 2025	☐
☐	PRAC Rapporteur AR	18 Aug 2025	14 Aug 2025	☐
☐	PRAC comments	22 Aug 2025	22 Aug 2025	☐
☐	CHMP comments	25 Aug 2025	25 Aug 2025	☐
☐	Updated PRAC Rapporteur AR	26 Aug 2025	n/a	☐
☐	Start of CHMP written procedure	2 Sept 2025	2 Sept 2025	☐
☐	PRAC outcome	2 Sept 2025	2 Sept 2025	☐
☒	CHMP Outcome	4 Sept 2025	4 Sept 2025	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

[3] Sections related to Risk Management Plan or on non-interventional PASS results. If PRAC advice was ad hoc requested by the CHMP, the relevant Attachment to the assessment report applies and has been endorsed by the PRAC.

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 27 February 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report from the non-interventional paediatric PASS 1160.307, listed as a category 3 study in the RMP. This is an observational study to evaluate the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age in routine clinical practice setting. The RMP version 42.0 has also been submitted.

The requested variation(s) proposed amendments to the amendments to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

Paediatric PASS

The MAH submitted the final report from the non-interventional paediatric PASS 1160.307, listed as a category 3 study in the RMP. This is a prospective, observational study to evaluate the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age in routine clinical practice setting. Consequential to the submission of the final report, the MAH updated the RMP (version 41.3), in which the study was removed from the PhV plan and relevant sections were updated accordingly.

The study objective could not be accomplished for feasibility reasons (0 patients were enrolled). The study aimed to enrol 50 patients under 2 years of age with VTE across 30 specialised sites in 10 European countries. After major efforts to identify appropriate sites who were willing to participate in the study, 19 sites across 9 countries finally agreed and were selected. The outcome of the site selection process revealed significant challenges.

As per the current indication, dabigatran can be used in children from the time they are able to swallow soft food, which is not applicable to a proportion of the target population of this study. An oral solution (OS) was never introduced to the markets due to a negative outcome of a human factor study as reported with the procedure EMEA/H/C/000829/II/0144. The OS formulation was subsequently deregistered in December 2023 following the approval of procedure EMEA/H/C/000829/II/0147/G. The absence of the OS led to the exclusion of neonates and young infants, who have the highest rate of VTE, which narrowed significantly the target patient population of this study.

In addition, based on the pre-screening outcomes of 16 sites involved in the study, dosage issues (no suitable dosage for low-weight patients) and financial considerations related to treatment costs and reimbursement issues were reasons for patients not enrolling in the study. Moreover, the MAH considers the availability of a competitive paediatric formulation of Xarelto for the target population might be another reason for pre-screening failure. Given the challenges, the MAH considers that any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues.

The primary objective of the study was to estimate the incidence of bleeding events among children under 2 years of age. Haemorrhage is an important identified risk in the RMP but the characterisation of this risk in the age group of children under 2 years is very limited which was the reason for the study being requested. Following de-registration of the oral solution in December 2023, children under 2 years of age who cannot swallow soft food are no longer part of the dabigatran indication. Consequently, the generation of further safety data in this sub-population of children below the age of 2 years is no longer required.

The characterisation of haemorrhage in children under 2 years who are able to swallow soft food is still lacking as the study failed to generate any new information. However, as use in the indication in children under 2 years is rare and competing treatment options are available (Xarelto oral suspension formulation for children including those under 2 years of age), the exposure in the population of interest seems very low. Therefore, the PRAC Rapporteur agrees with the MAH that any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues and therefore not considered appropriate. Further safety monitoring of dabigatran in the special population of children below the age of 2 via routine PhV is considered sufficient.

The final study report and the consequential changes to the RMP are endorsed.

Other issues in the RMP (not based on proposed changes)

Characterisation of risks

The PRAC Rapporteur noted that the characterisation of the important identified risk haemorrhage in module SVII.3.1 is was extensive (88 pages) and challenging to interpret. Based on request, the MAH provided an amended RMP presenting a much more concise and reader-friendly characterisation of the risk, which is endorsed.

Missing information

In addition, the PRAC Rapporteur questioned whether it is still appropriate to maintain the missing information "Patients aged 0 to 2 years who were born prematurely" in the RMP. Following the deregistration of the oral solution formulation, exposure in this population is expected to be negligible. This is supported by the experience from the paediatric PASS in which no patient could be enrolled and a search of the MAH's safety database in which no spontaneous case in this population could be identified. In addition, the data from clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. There are no risk management activities such as additional PhV activities to gain further knowledge, nor additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures, which would warrant maintaining this MI in the RMP. Therefore, the PRAC Rapporteur agrees that the missing information "Patients aged 0 to 2 years who were born prematurely" can be removed from the RMP.

The benefit-risk balance of Pradaxa remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.13	C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Variation type II

Submission of the final report from the non-interventional paediatric PASS 1160.307, listed as a category 3 study in the RMP. This is an observational study to evaluate the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age in routine clinical practice setting. The RMP version 42.0 has also been submitted.

☒is recommended for approval.

Amendments to the marketing authorisation

The Variation leads to no amendments to the terms of the Community Marketing Authorisation.

The variation requires amendments to the Risk Management Plan.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Submission of the final report from the non-interventional paediatric PASS 1160.307, listed as a category 3 study in the RMP. This is an observational study to evaluate the safety of dabigatran etexilate for the treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age in routine clinical practice setting. The RMP version 41.3 has also been submitted.

Summary

Please refer to Scientific Discussion EMA/VR/0000256456

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Limited evidence is available for safety of dabigatran anticoagulation in children from birth to < 2 years. This is also the age group that demonstrates the most marked differences from adults in haemostaseology. Thus, the post-authorization data collection in study 1160.307 was planned to collect more safety data of dabigatran in children under 2 years of age including the age-specific drug product formulation "oral liquid formulation" from birth up to 1 year and coated granules for children who can swallow them on food.

The PASS study 1160.307 was agreed with EMA in the frame of the Extension of Marketing Authorization of Pradaxa to register the pediatric formulations of Pradaxa (procedure EMEA/H/C/00829/X/122/G). It is listed as an additional pharmacovigilance activity in the RMP category 3, and it is entitled: "Safety of dabigatran etexilate (DE) for treatment of venous thromboembolism (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a prospective European non- interventional cohort study based on new data collection". The protocol of the PASS was submitted with procedure EMEA/H/C/000829/MEA/051. The following milestone date for submission of the final report of the PASS is stated in the RMP: "estimated in Q2 2025". Therefore, the present submission is compliant with the milestone date.

6. Clinical Safety aspects

6.1. Methods – analysis of data submitted

The objective of the study 1160.307 was to evaluate the safety of DE for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting.

The study sample size was based on the anticipated usage of dabigatran for acute VTE treatment and prevention of recurrent VTE. A target sample size of 50 evaluable patients was planned to be enrolled from approximately 30 paediatric sites in 10 EU/EEA countries over a 2-year period.

Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors were considered as one unique patient.

Paediatric patients under 2 years of age, who could have been considered for anticoagulation with DE due to acute VTE, were expected to be treated in neonatology, paediatric general surgery, cardiac surgery, or intensive care units. Paediatric patients with anticoagulation with DE for the prevention of recurrent VTE were expected to be evaluated mostly by paediatric haematologists in paediatric haematology units.

After major efforts to identify appropriate sites who were willing to participate in the study, 19 sites across 9 countries finally agreed and were selected.

During the approximate 1.5-year enrolment period in this study every effort was made to support investigators to enroll paediatric patients requiring dabigatran anticoagulation. These efforts respecting the non-interventional character of the study included communications with investigators using digital resources and face to face communications, presentation of the results and enrolment strategies of the previous published studies on DE, focused on early age children.

6.2. Results

The study encountered significant recruitment challenges for site identification and patient enrolment:

- Lack of availability of the oral solution (OS) formulation of Pradaxa particularly important for population of infants and neonates. This formulation was never introduced to the markets due to a negative outcome of a human factor study as reported with the procedure EMEA/H/C/000829/II/0144. The OS formulation was subsequently deregistered in December 2023 following the approval of procedure EMEA/H/C/000829/II/0147/G. The absence of the OS led to the exclusion of neonates and young infants, In the bimodal age distribution of pediatric VTE, the early peak (age < 1 year) refers to critically ill neonates/infants and children with CVAD- / central line -related VTE, while the rise during adolescence generally reflects the development of adult VTE risk factors and the use of contraception in female adolescents [P94-81556; R20-2562; P21-05936].

As the OS formulation indicated for children < 1 year was not launched, one major group of the pediatric VTE indication had to be cancelled, and the study had to be performed using only the coated granules formulation of Pradaxa.

- New competing treatment options (i.e. Xarelto® (rivaroxaban) oral suspension) that have decreased uptake of the granule formulation of Pradaxa.

- An overall low incidence of VTE in paediatric patients. VTE is a rare event in children (1 in 100 000) compared to adults (1 in 1000) [R09-4866, R06-2301, P94-81556]. Some authors have described VTE as an increasing problem in hospitalized children, ranging from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to the current 30 to 58 events per 10,000 pediatric hospital admissions [P94-81556; P20-06834; R13-4251; R20-2562]. However, some of these publications come with significant limitations. For example, the main limitation of the study by Raffini et al [R13-4251] is that it is not population-based. All "rates" of VTE reported in the manuscript thus do not reflect true epidemiological rates (i.e. number of events divided by persons or person-time at risk), but rather a proportional measure of VTE hospitalizations among all hospitalisations.

These factors collectively contributed to challenges in site selection and investigator engagement, and finally affected the study's ability to recruit the target patient population negatively.

Due to the very low prescribing rates of coated granules, generating data from real world use has not been fruitful, no patients could be screened/enrolled into study 1160.307.

6.3. Discussion

See section 7.3.

7. Non-interventional Post-Authorisation Safety Study (PASS) results

7.1. Methods – analysis of data submitted

Rationale and background

Dabigatran is a direct thrombin inhibitor that is effective for treatment of VTE and prevention of recurrent VTE in adults. However, the concept of developmental haemostasis precludes complete extrapolation of adult efficacy and safety data to children, particularly those of the youngest age group of neonates and infants. In hospitalised children, a significant increase of 70% in VTEs has been noted.

Anticoagulation agents commonly used in children present with frequent challenges, and there is a high unmet need for age-appropriate treatment options to manage VTEs in children. For adequate anticoagulation, it is essential to balance the risk of thromboembolic events with the risk of bleeding. The clinical results of dabigatran anticoagulation in children with VTEs are based on a limited number of patients. However, the overall safety and efficacy of dabigatran in this population was supported by a remarkable consistency across all age groups and comparable to the clinical outcomes in adult patients with VTE who were treated with dabigatran. However, limited evidence is available for the safety of dabigatran anticoagulation in children from birth to < 2 years. This is also the age group that demonstrates the most marked differences from adults in haemostaseology. Thus, this non-interventional cohort study was planned to obtain more safety data of dabigatran in children under 2 years of age. The results from this Post-Authorisation Safety Study (PASS) were planned to be interpreted in the context of the findings from the paediatric clinical development program.

Research question and objectives

Limited safety data are available for DE in children from birth to < 2 years of age for the treatment of acute VTE treatment and prevention of recurrent VTE.

The objective of this study was to evaluate the safety of DE for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting.

Primary objective:

- To estimate the incidence of any bleeding event defined as Major Bleeding Event (MBE) or Non-Major Bleeding Event (Non- MBE) among the children under 2 years of age on DE administration.

Secondary objective:

- To estimate the incidence of Adverse Events (AEs).
- To estimate the incidence of Serious Adverse Events (SAEs).

Further objective:

- To assess acceptability and tolerability of paediatric formulation

Study design

This was a prospective, non-interventional, European, multinational, multicenter cohort study based on newly collected data of paediatric patients anticoagulated with DE for acute VTE treatment or prevention of recurrent VTE.

The study was designed to collect and evaluate DE safety in the context of routine anticoagulation care provided in the European Economic Area (EEA) member states for children under 2 years of age. The duration of the study was planned to be up to 2 years from the date of study initiation with the goal to enrol 50 evaluable patients under DE administration. Approximately 10 EEA member states were planned to engage in this study.

Safety outcomes were planned to be collected for a period of up to 3 months from the day of DE initiation defined as the index date for the treatment of acute VTE and up to 6 months from the index date for prevention of recurrent VTE. DE acute VTE treatment could have been followed by secondary VTE prevention due to unresolved VTE risk factors. The overall duration of the study observational period for any patient was not to exceed a 6-month period of anticoagulation. If acute treatment was followed by anticoagulation for prevention of recurrent VTE, the maximal period in the study was planned to be 6 months. In this situation, the index date for start of anticoagulation for prevention of

recurrent VTE was to be based on investigator judgment or after 3 months of treatment for acute VTE, whichever occurred earlier. Anticoagulation of more than 6 months' duration, if required due to the presence of unresolved VTE risk factors, was not planned to be covered in this study setting.

The study was observational and did not entail any change in prescribing pattern or management strategies, which were left to the discretion of the treating physician. According to the Non-Interventional Study concept no special evaluation procedure was required.

Setting

Study periods

After informed consent patients were planned to be screened for enrolment into the study. A Screening Log to ensure consecutive screening and enrolment was planned to be used so that all eligible patients under 2 years with an indication for anticoagulation were identified.

If a patient met all study entry criteria, a baseline part of the Screening/Baseline visit was planned to be conducted, and the patient was to enter an observational study period.

The observational study period for a patient was defined as the time period from the index date (initiation of DE administration) onwards up until DE administration discontinuation + 3 days of Residual Effect Period (REP) or switch to other anticoagulation therapy + 3 days of REP or planned end of the 6 months' observation time, whichever occurred earlier. It was not planned to follow patients outside the observational period.

A patient who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors was to be considered as one unique patient. However, safety outcomes of each anticoagulation period were planned to be evaluated within the corresponding cohort.

Data collection visits were planned for both VTE treatment and prevention of recurrent VTE groups as follows:

- Baseline part of Screening/Baseline visit: index date (initiation of DE administration).
- Follow-up visit(s):
    - At approx. 6 weeks or 3 months after initiation of DE administration for children treated for acute VTE, based on investigator judgment.
    - At approx. 3 or 6 months of DE administration, for prevention of recurrent VTE group based on investigator judgment.

Patients who continued secondary VTE prevention after acute VTE treatment were planned to have 2 follow-up visits: the first at the end of DE treatment for acute VTE, and the second at discontinuation of DE for secondary VTE prevention or after a total of 6 months of DE administration, whichever occurred first. The Final Study Visit was defined as a follow-up visit conducted after the end of the observational period.

Study sites

The PASS was intended to be available to paediatric hospitals and paediatric departments of EEA member states, where VTE paediatric patients under 2 years of age were treated, depending on country regulations and requirements. Approximately 30 paediatric study sites with experience in VTE anticoagulation treatment and prevention were planned to be selected and initiated by Q4 2022. Every effort was made to identify sites where paediatric use of DE was available.

The selection of study sites for the 1160.307 study was focused on specialised paediatric units treating neonates, infants, and young children.

Neonates and infants with acute VTE requiring DE administration were localised in the following paediatric units:

- neonatology departments, where target conditions were umbilical thrombosis, cerebral vein thrombosis, central line related-VTE, etc.
- paediatric surgery, paediatric cardiology, paediatric cardio-surgery, intensive care units, and paediatric haematology departments where target conditions were central line/implantable devices related- VTE, cyanotic congenital heart disease, venous malformations, leukaemias etc.

Patients who required anticoagulation for secondary VTE prevention were expected to be evaluated mostly in paediatric haematology, paediatric cardiology, and paediatric cardio-surgery departments.

During the approximate 1.5-year enrolment period every effort was made to support investigators to enrol paediatric patients requiring dabigatran anticoagulation in this study. These efforts taking into account the non- interventional character of the study included communications with investigators using digital resources and face to face communications, and presentation of the results and enrolment strategies of the previous published studies on DE, focused on early age children.

Subjects and study size, including dropouts

The study sample size was based on the anticipated usage of DE for VTE treatment and prevention. Overall, 50 patients under 2 years of age were planned to be enrolled in the study. Approximately 30 paediatric study sites with experience in VTE anticoagulation treatment and prevention were planned to be selected for the PASS in EEA member states. Approximately 10 EEA member states were planned to engage in this study.

Paediatric patients under 2 years of age, who could have been considered for anticoagulation with DE due to acute VTE, were expected to be treated in neonatology, paediatric general surgery, cardiac surgery, or intensive care units. Paediatric patients with anticoagulation with DE for the prevention of recurrent VTE were expected to be evaluated mostly by paediatric haematologists in paediatric haematology units.

Inclusion criteria:

- Written informed consent from parents/care givers,
- Children from birth to < 2 years of age,
- Initiation of DE administration according to the EU DE Summary of Product Characteristics (SmPC):
    - for treatment of acute VTE or/and
    - prevention of recurrent VTE due to presence of an unresolved clinical VTE risk factor(s).

Exclusion criteria:

- Participation in any randomised controlled trial or use of investigational product,
- Any contraindications to DE according to the EU SmPC

Safety outcomes were planned to be collected from 50 patients overall anticoagulated with DE for acute VTE treatment and/or prevention of recurrent VTE due to presence of unresolved clinical VTE risk factor(s).

The paediatric population was planned to be accordingly stratified into 2 cohorts:

- Children anticoagulated with dabigatran due to acute VTE treatment.
- Children anticoagulated with dabigatran for prevention of recurrent VTE due to the presence of an unresolved VTE clinical risk factor.

Patients who completed acute VTE treatment and continued DE anticoagulation due to unresolved VTE risk factors were to be considered as one unique patient. However, each anticoagulation period was planned to be evaluated within the corresponding cohort.

Variables and data sources

Detailed information on paediatric patients under 2 years of age and DE administration was planned to be collected as follows:

At Screening/Baseline:

- Demographics (e.g., age, weight, gender, race, country),
- Hospitalisation details, type of paediatric department (e.g., neonatology, cardio-surgery, Intensive Care Unit, haematology, etc.) and procedures related to VTE diagnostic modalities,
- Medical history including concomitant medications history (administered within 14 days prior to informed consent),
- Baseline conditions,
- Acute VTE characteristics as type of VTE, symptomatic/asymptomatic, location; VTE characteristics obtained according to standard diagnostic modalities and local protocols,
- Available characteristics of the most recent VTE event (as specified above) for prevention of recurrent VTE group,
- Presence of post-thrombotic syndrome (PTS); if PTS present, diagnostic scale used and score should be indicated,
- VTE clinical risk factor(s),
- Initial DE dosage and formulation if a patient initiated DE treatment.

At Follow up:

- Incidence of any bleeding event defined as MBE or Non-Major Bleeding Events (Non-MBE) including location(s),
- Incidence of AEs/SAEs,
- Concomitant treatment and procedures,
- Any changes in DE dosage(s) and formulation with corresponding age and weight,
- Duration of DE administration,
- Acceptability and tolerability of paediatric DE formulation; acceptability was defined as the overall ability and willingness of the patient to use the medicinal product as intended;

tolerability was measured as premature treatment discontinuation, and adherence to trial medication.

The safety data were planned to be evaluated based on the study observational period, i.e., from the index date (initiation of DE administration) onwards up until DE administration discontinuation + 3 days of REP or switch to other anticoagulation therapy + 3 days of REP or planned end of the 6 months' observation time, whichever occurred earlier.

Patients who continued secondary VTE prevention after acute VTE treatment were planned to have 2 follow-up visits: the first at the end of DE treatment for acute VTE, and the second at discontinuation of DE for secondary VTE prevention or after a total of 6 months of DE administration, whatever occurred first.

All data were to be obtained by qualified clinicians according to the standard medical practice.

Newly collected data and/or data collected from medical records were planned to be entered by the site directly in an electronic data capture (EDC) system via an Internet portal.

All sites were to be fully trained for using the EDC system and BI AE/SAE reporting procedure. It was to be the PI's responsibility to ensure for his/her site the accuracy of the data provided to the program by any site staff that were trained for the program data collection.

7.2. Results

This study aimed to enroll 50 patients under 2 years of age with VTE across 30 specialised sites in 10 European countries. After major efforts to identify appropriate sites who were willing to participate in the study 19 sites across 9 countries finally agreed and were selected.

The study enrolment was finally discontinued at the end of the pre-defined enrolment period on 31 May 2024; no patients could be screened/enrolled.

The outcome of the site selection process revealed significant challenges (out of 133 sites approached across all countries, only 24 expressed interest, with 87 declining and 22 non-responsive), particularly in Germany (out of 93 sites approached, only 8 expressed interest).

Pre-screening was conducted at 16 sites and not conducted at 3 sites. The primary factors precluding patient enrolment were dosage issues (no suitable dosage was available for low-weight patients), swallowing difficulties (no OS formulation was available), and financial considerations related to treatment costs and reimbursement issues. Additionally, the availability of a competitive paediatric formulation of Xarelto for the target population might be another reason for pre-screening failure.

Parexel was responsible for conducting qualification calls and evaluating sites based on criteria including interest in the study, PI experience, access to the target patient population, and agreement to study rules. The initial plan included 30 sites with 4 backups, but modifications were made. During the feasibility study, Belgium, France, and Poland were cancelled (no sites in these countries agreed to participate in the study), and one site each in Denmark and Austria agreed to participate in the study and were added.

The feasibility process involved searching physician and clinic websites, contacting potential investigators, and preparing confidentiality agreements. Rescue feasibility efforts were implemented when initial approaches proved challenging, including searching real-world databases and reaching out to relevant medical societies.

7.3. Discussion

The study encountered significant recruitment challenges for site identification and patient enrolment:

1) Lack of availability of the oral solution (OS) formulation particularly important for population of infants and neonates. This formulation was never introduced to the markets due to a negative outcome of a human factor study as reported with the procedure EMEA/H/C/000829/II/0144. The OS formulation was subsequently deregistered in December 2023 following the approval of procedure EMEA/H/C/000829/II/0147/G. The absence of the OS led to the exclusion of neonates and young infants, who have the highest rate of VTE, which narrowed significantly the target patient population of this study.
2) Insufficient scientific interest among potential investigators in light of the availability of an alternative paediatric treatment, namely Xarelto® (rivaroxaban), for the target population.
3) An overall low incidence of VTE in paediatric patients.

Additionally, some PIs expressed hesitation in prescribing DE due to limited clinical experience with the drug. These factors collectively contributed to challenges in site selection and investigator engagement, and potentially affected the study's ability to recruit the target patient population negatively.

Pre-screening was conducted at 16 sites; however, patient enrolment was primarily impeded by 1) dosage issues (no suitable dosage was available for low-weight patients); 2) swallowing difficulties (no OS formulation was available); 3) financial considerations, including treatment costs and reimbursement issues in some countries.

The study enrolment was finally discontinued on 31 May 2024, at the end of the pre-defined enrolment period; no patients could be screened/enrolled. Considering the multi-factorial reasons leading to the infeasibility of conducting this study, a further prolongation of the screening/enrolment phase would not have been productive.

In conclusion, the objective of this PASS which was to evaluate the safety of DE for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting could not be accomplished for feasibility reasons. The availability of alternative paediatric treatments on the market, current clinical practices, investigator preferences, and the non-availability of the DE OS formulation collectively presented significant obstacles. Given these challenges, any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues.

PRAC Rapporteur's Comment

The study objective to evaluate the safety of dabigatran for the treatment of VTE and prevention of recurrent VTE in children from birth to < 2 years of age in a routine clinical practice setting could not be accomplished for feasibility reasons.

As per the current indication, dabigatran can be used in children from the time they are able to swallow soft food, which is not applicable to a proportion of the target population of this study. An oral solution (OS) was never introduced to the markets due to a negative outcome of a human factor study as reported with the procedure EMEA/H/C/000829/II/0144. The OS formulation was subsequently deregistered in December 2023 following the approval of procedure EMEA/H/C/000829/II/0147/G. The absence of the OS led to the exclusion of neonates and young infants, who have the highest rate of VTE, which narrowed significantly the target patient population of this study.

In addition, based on the pre-screening outcomes of the sites involved in the study, dosage issues (no suitable dosage for low-weight patients) and financial considerations related to treatment costs and reimbursement issues were reasons for patients not enrolling in the study. Moreover, the MAH considers the availability of a competitive paediatric formulation of Xarelto for the target population might be another reason for pre-screening failure.

Given the challenges, the MAH considers any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues.

The final study report is considered acceptable.

8. PRAC advice

N/A

9. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 41.3 with this application. Following requests for an updated RMP, the MAH submitted RMP version 42.0. The (main) proposed RMP changes (for both versions in relation to the latest approved version) were the following:

9.1. Safety Specification

NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Removal of the missing information "Patients aged 0 to 2 years who were born prematurely"

Rationale for removal

Following the complete deregistration of the Pradaxa oral solution formulation in the countries where it was registered (EU countries in December 2023 with procedure no. EMEA/H/C/000829/II/0147/G, and Great Britain in May 2024), Boehringer Ingelheim considers that it will be unlikely that a significant number of children between 0-2 years of age who are able to swallow soft food, especially premature ones, will be treated with Pradaxa, taking into account the results of PASS 1160-307, the existence of suitable alternative in the market (rivaroxaban, oral solution), the overall low incidence of VTE in paediatric patients, and the absence of post-marketing data for this specific subpopulation.

Furthermore, the Pradaxa paediatric clinical development programme is complete, and Boehringer Ingelheim is not planning any further studies in this specific subpopulation.

Safety data from the Pradaxa clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. No data exists concerning children 0 to 2 years of age who were born prematurely. However, no significant difference is expected.

Based on this, Boehringer considers that there is no need to keep "Patients aged 0 to 2 years who were born prematurely" as missing information and proposes that this risk is removed from the list of safety concerns of the RMP.

Boehringer will continue to monitor the safety of patients, including this subpopulation, through routine pharmacovigilance activities.

PRAC Rapporteur's Comment

The MAH proposes the removal of the missing information "Patients aged 0 to 2 years who were born prematurely". The MAH's justification is acknowledged. Following the deregistration of the oral solution formulation, exposure in this population is expected to be negligible. This is supported by the experience from the paediatric PASS in which no patient could be enrolled and a search of the MAH's safety database in which no spontaneous case in this population could be identified. In addition, the data from clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. There are no risk management activities such as additional PhV activities to gain further knowledge, nor additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures, which would warrant maintaining this MI in the RMP.

The PRAC Rapporteur agrees that the missing information "Patients aged 0 to 2 years who were born prematurely" can be removed from the RMP.

DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

- Section SVII.3.1.1 (important risk "Haemorrhage") has been streamlined to provide an overview of the risk characterisation by indication across clinical trials and relevant post-marketing studies. The request of the characterisation of the risk in children has been addressed.
- A summary of the results of the completed PASS 1160-0307 has been included in the section SVII.3.1.1 related to the indication of "Paediatric VTE", as requested.

PRAC Rapporteur's Comment

As requested, an updated more concise characterisation of the important identified risk Haemorrhage has been provided. This is acceptable.

Summary of safety concerns

Important identified risks	Haemorrhage
Important potential risks	None
Missing information	Paediatric patients with renal dysfunction (eGFR <50ml/min)[1]

[1]This safety concern is only valid in countries where the paediatric indication is approved.

PRAC Rapporteur's Comment

Based on the justification provided above, the MAH has removed the missing information "Patients aged 0 to 2 years who were born prematurely" from the RMP. This is acceptable.

9.2. Pharmacovigilance plan

There are no additional pharmacovigilance activities.

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances None				
Category 3 – Required additional pharmacovigilance activities None.				

PRAC Rapporteur's Comment

Based on the submission of the final study report for study 1160.307 (see section 7.), the MAH deleted the study from the PhV plan and updated relevant parts of the RMP accordingly. These changes are acceptable.

The primary objective of the study was to estimate the incidence of bleeding events among children under 2 years of age. Haemorrhage is an important identified risk in the RMP but the characterisation of this risk in the age group of children under 2 years is very limited which was the reason for the study being requested. Following de-registration of the oral solution in December 2023, children under 2 years of age who cannot swallow soft food are no longer part of the dabigatran indication. Consequently, the generation of further safety data in this sub-population of children below the age of 2 years is no longer required.

The characterisation of haemorrhage in children under 2 years who are able to swallow soft food is still lacking as the study failed to generate any new information. However, as use in the indication in children under 2 years is rare and competing treatment options are available (Xarelto oral suspension formulation for children including those under 2 years of age), the exposure in the population of interest seems very low. Therefore, the PRAC Rapporteur agrees with the MAH that any future attempt to conduct a similar study is highly likely to encounter similar feasibility issues and therefore not considered appropriate. Further safety monitoring of Pradaxa in the special population of children below the age of 2 via routine PhV is considered sufficient.

Overall conclusions on the PhV Plan

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

9.3. Elements for a public summary of the RMP

Important identified risk Haemorrhage	
Evidence for linking the risk to the medicine	Anticoagulation bears an inherent risk of haemorrhage. Based on clinical and post-marketing data, haemorrhage was defined as an important identified risk for Pradaxa. Dabigatran (the active substance of Pradaxa) is eliminated through the kidneys, and kidney function diminishes with increasing age. Therefore, the rates of haemorrhages depend on the dose and are related to renal (kidney) failure and age.
Risk factors and risk groups	The risk of haemorrhages with Pradaxa increases with declining kidney function. Kidney function diminishes with age. Therefore, the elimination of dabigatran may be reduced, and dabigatran blood levels may be increased, in elderly patients and in patient with reduced kidney function. As a consequence, the risk of bleeding is increased in these patients. The highest rates occur in the very elderly (age >75 years) with poor kidney function.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 • PL Sections 2, 3, and 4 Other risk minimisation measures: • Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation effect of dabigatran case of emergency surgery or urgent procedures for situations of life-threatening or uncontrolled bleeding. A paediatric investigation plan for idarucizumab has been completed. In paediatric patients for whom the specific reversal agent cannot be used, haemodialysis can remove dabigatran. Additional risk minimisation measures: • Prescriber guide and patient alert card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Other studies in post-authorisation development plan

There are no studies required for Pradaxa.

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

9.4. Annexes

The annexes have been updated appropriately.

9.5. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

10. Request for supplementary information

10.1. Major objections

RMP aspects

None

10.2. Other concerns

RMP aspects

1. The PRAC Rapporteur noted that the characterisation of the important identified risk haemorrhage in module SVII.3.1 is very extensive (88 pages) and challenging to interpret. Instead of presenting detailed information per study, the most important findings for the characterisation of the risk should be synthesised. Moreover, the characterisation of the risk in children and specifically in children below the age of 2 years should be converged so the reader can get a quick overview of the risk in this age group. While study 1160.307 did not further the characterisation of the risk, it is considered meaningful to mention the study in this module nonetheless. More broadly, the MAH is asked to update Module SVII.3 in accordance to the guidance provided in GVP V (rev 2) and its accompanying EMA/164014/2018 Rev.2.0.1., and follow the following concepts:

    - "*Consider which information will add value to the readers' understanding of the safety profile of the medicinal product and how best to interpret and manage the important identified risks as well as the uncertainties surrounding the information available. Please focus the document accordingly."*
    - "*The safety profile of the product should be concisely presented*."

- "*The amount of information, particularly in RMP part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its life cycle*."
- "*Information in the RMP should be provided in enough detail whilst avoiding unnecessary text that distracts from the key issues to be considered for risk management of the product*."

2. Based on the final results of the paediatric PASS, the use of dabigatran in patients below the age of 2 seems to be very limited and it is therefore questionable whether it is appropriate to maintain the missing information "Patients aged 0 to 2 years who were born prematurely" in the RMP. Moreover, there are no additional PhV activities to gain further knowledge, no additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures. The MAH is asked to discuss the appropriateness of maintaining "Patients aged 0 to 2 years who were born prematurely" as missing information in the RMP. If possible, this should be informed by data on the use of dabigatran in this population (and in patients below the age of 2 in general). As applicable, the RMP should be updated accordingly.

11. Assessment of the responses to the request for supplementary information

11.1. Major objections

None

11.2. Other concerns

RMP aspects

1. The PRAC Rapporteur noted that the characterisation of the important identified risk haemorrhage in module SVII.3.1 is very extensive (88 pages) and challenging to interpret. Instead of presenting detailed information per study, the most important findings for the characterisation of the risk should be synthesised. Moreover, the characterisation of the risk in children and specifically in children below the age of 2 years should be converged so the reader can get a quick overview of the risk in this age group. While study 1160.307 did not further the characterisation of the risk, it is considered meaningful to mention the study in this module nonetheless. More broadly, the MAH is asked to update Module SVII.3 in accordance to the guidance provided in GVP V (rev 2) and its accompanying EMA/164014/2018 Rev.2.0.1., and follow the following concepts:

    - "*Consider which information will add value to the readers' understanding of the safety profile of the medicinal product and how best to interpret and manage the important identified risks as well as the uncertainties surrounding the information available. Please focus the document accordingly."*
    - "*The safety profile of the product should be concisely presented*."
    - "*The amount of information, particularly in RMP part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its life cycle*."
    - "*Information in the RMP should be provided in enough detail whilst avoiding unnecessary text that distracts from the key issues to be considered for risk management of the product*."

Summary of the MAH's response

To address this request, the RMP for Pradaxa has been updated (RMP version 42.0) as follows:

- Section SVII.3.1.1 (important risk "Haemorrhage") has been streamlined to provide an overview of the risk characterisation by indication across clinical trials and relevant post-marketing studies. The request of the characterisation of the risk in children has been addressed.
- A summary of the results of the completed PASS 1160-0307 has been included in the section SVII.3.1.1 related to the indication of "Paediatric VTE", as requested.
- The title page and Appendix 8 have been updated with administrative information related to the RMP version and the content of the update.

Assessment of the MAH's response

As requested, the characterisation of the risk section for the important identified risk "Haemorrhage" has been updated. The present proposal is much more concise, reader-friendly and considered in line with the recommendations provided in EMA/164014/2018 Rev.2.0.1. Moreover, the characterisation of the risk in children has been integrated adequately and information about the completed PASS 1160-0307 has been included.

The changes are acceptable.

Conclusion

Issue considered resolved.

2. Based on the final results of the paediatric PASS, the use of dabigatran in patients below the age of 2 seems to be very limited and it is therefore questionable whether it is appropriate to maintain the missing information "Patients aged 0 to 2 years who were born prematurely" in the RMP. Moreover, there are no additional PhV activities to gain further knowledge, no additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures. The MAH is asked to discuss the appropriateness of maintaining "Patients aged 0 to 2 years who were born prematurely" as missing information in the RMP. If possible, this should be informed by data on the use of dabigatran in this population (and in patients below the age of 2 in general). As applicable, the RMP should be updated accordingly.

Summary of the MAH's response

Background
With the approval of a new pediatric indication for Pradaxa ("*Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age"*, referred to as paediatric VTE, approved by EMA on 11 Jan 2021 with Procedure no. EMEA/H/C/000829/X/0122/G), the safety risk "Patients aged 0 to 2 years who were born prematurely" was added to the list of Safety Concerns of the Risk Management Plan as Missing Information.
The population in need for further characterization was defined as patients 0 to 2 years of age whose gestational age at birth was <37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards). The source of evidence for this missing information was very limited because the concerned population was excluded from Pradaxa pediatric clinic trials. Consequently, due to the lack of experience, the anticipated risk in this patient population is not known.

Summary of safety data from Pradaxa in paediatric population

Table 1 presents an overview of the clinical trials included in the evaluation of efficacy/safety of the Pradaxa clinical development paediatric programme.

Table 1 Overview of trials included in the evaluation of efficacy/safety

Trial no. (Phase) [Reference]	Trial design	N[1]	Formulation of DE	DE dose; duration of treatment	Trial population
1160-0088 (IIa) [U12-3378]	Open label, single arm	9	Capsules	Weight-adjusted dose; 3 days bid	Adolescents (12 to <18 years)
1160-0089 (IIa) [c09069268]	Open label, single arm	18	Oral solution	Age- and weight-adjusted dose; single dose/ 3 days bid[2]	1 to <12 years
1160-0105 (IIa) [c09085437]	Open label, single arm	8	Oral solution	Age- and weight-adjusted dose; single dose	0 to <1 year
1160-0106 (IIb/III), [c29773859]	Open label, randomised, active-controlled (standard of care)	266	Oral solution, granules[3], capsules	Age- and weight-adjusted dose and formulation; 3 months	0 to <18 years
1160-0108 (III), [c29754273]	Open label, single arm	213	Oral solution, granules[3], capsules	Age- and weight-adjusted dose and formulation; treatment until resolution of clinical risk factor (max.: 12 months)	0 to <18 years

[1] Number of treated patients. Rollover patients are counted in each trial where they participated.

[2] As agreed with the PDCO, the multiple dosing schedule was changed to a single dose of DE during the trial.

[3] For consistency with the CTPs, the term 'pellets' is used in the CTRs. It refers to 'coated granules in sachets' or short 'granules'

The overall safety and efficacy of Pradaxa (dabigatran etexilate (DE)) in children are supported by remarkable consistency within all age groups and with the clinical outcomes in adult patients with VTE who were treated with DE, despite the smaller number of children enrolled in paediatric trials [P13-16985, P19-11322, P20-07911]. In total, 363 children were treated with dabigatran etexilate (DE), of which 44 (12.1%) were between 0-2 years of age (Table 2).

Table 2 Disposition of patients - unique DE treated set of the combined paediatric trials

	Birth to <2 years	**2 to <12 years**	**12 to <18 years**	**Total**
Treated, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Completed planned observation time[1]	41 (93.2)	81 (94.2)	219 (94.0)	341 (93.9)
Premature trial discontinuation	3 (6.8)	5 (5.8)	14 (6.0)	22 (6.1)
Other	1 (2.3)	2 (2.3)	7 (3.0)	10 (2.8)
Non−compliant with protocol	2 (4.5)	0	2 (0.9)	4 (1.1)
Consent withdrawn	0	2 (2.3)	2 (0.9)	4 (1.1)
Lost to follow−up	0	1 (1.2)	1 (0.4)	2 (0.6)
AE other	0	0	2 (0.9)	2 (0.6)
Source of patients, N (%)				
Participated in 1160.88	0	0	9 (3.9)	9 (2.5)
Participated in 1160.89	6 (13.6)	12 (14.0)	0	18 (5.0)
Participated in 1160.105	8 (18.2)	0	0	8 (2.2)
Participated in 1160.108 only	8 (18.2)	27 (31.4)	87 (37.3)	122 (33.6)
Participated in 1160.106 only	21 (47.7)	31 (36.0)	63 (27.0)	115 (31.7)
Rollover patients from 1160.106 to 1160.108[2]	1 (2.3)	16 (18.6)	74 (31.8)	91 (25.1)

[1] Planned observation time: the time from the last intake of trial medication until the planned follow-up visit.

[2] For patients treated with SoC in trial 1160.106 and with DE in trial 1160.108, age at informed consent in trial 1160.108 was taken for the assignment to age strata. Therefore, patient numbers differ from the 1160.106 CTR, which took age at informed consent in trial 1160.106 as basis for age group assignment.

Source data: [c31325825, Tables B.1: 1 and B.2: 1]

Regarding the main safety endpoints (Table 3), the rate of recurrent VTE in the paediatric programme was low and consistent with the estimated population incidence. Bleeding events were mostly categorised as minor and were more frequent in the oldest age stratum than in younger children. Specifically, in children aged 0-2, no recurrent VTE occurred, whereas 7 bleeding events were observed. No deaths were reported across all pediatric trials.

Table 3 Recurrent VTEs and bleeding events on-treatment - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated patients, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Patients with recurrent VTE [1]	0	0	9 (3.9)	9 (2.5)
Patients with bleeding events [1, 2]	7 (15.9)	12 (14.0)	64 (27.5)	83 (22.9)
Major	1 (2.3)	1 (1.2)	5 (2.1)	7 (1.9)
CRNM	0	2 (2.3)	3 (1.3)	5 (1.4)
Minor	6 (13.6)	10 (11.6)	59 (25.3)	75 (20.7)

[1] Data based on adjudication-confirmed events (trials 1160.106 and 1160.108) or investigator-reported events (trials 1160.88, 1160.89, and 1160.105)

[2] A patient may be counted in more than 1 bleeding category

Source data: [c31325825, Table B.4: 1]

Overall, 267 patients (73.6%) had at least 1 AE during the on-treatment period, with 29 patients (8.0%) having an AE of severe intensity. There were no significant differences in the number of adverse events between age groups (Table 4).

Table 4 Adverse event overall summary on-treatment - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated patients, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Patients with any AE	24 (54.5)	57 (66.3)	186 (79.8)	267 (73.6)
Patients with severe AEs	3 (6.8)	6 (7.0)	20 (8.6)	29 (8.0)
Patients with investigator defined drug-related AEs	6 (13.6)	13 (15.1)	68 (29.2)	87 (24.0)
Patients with other significant AEs (according to ICH E3)	3 (6.8)	2 (2.3)	15 (6.4)	20 (5.5)
Patients with AEs leading to discontinuation of trial treatment	4 (9.1)	5 (5.8)	18 (7.7)	27 (7.4)
Patients with protocol-specified AEs of special interest	0	1 (1.2)	2 (0.9)	3 (0.8)
Patients with serious AEs[1]	3 (6.8)	11 (12.8)	41 (17.6)	55 (15.2)
Fatal	0	0	0	0
Immediately life-threatening	0	0	4 (1.7)	4 (1.1)
Disability/incapacity	0	0	0	0
Required hospitalisation	2 (4.5)	10 (11.6)	33 (14.2)	45 (12.4)

Prolonged hospitalisation	1 (2.3)	1 (1.2)	6 (2.6)	8 (2.2)
Congenital anomaly	0	0	0	0
Other	1 (2.3)	5 (5.8)	9 (3.9)	15 (4.1)

[1] A patient may be counted in more than 1 seriousness criterion.

Source data: [c31325825, Table B.5: 1]

Serious AEs during the on-treatment period were reported for 55 patients (15.2%), all of them in the Phase IIb/III trials. Few PTs were reported for more than 1 patient in total, see Table 5. No patient died on-treatment with DE.

Table 5 Most frequent serious adverse events on-treatment (PTs reported overall for more than 1 patient) - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated patients, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Patients with any SAE	3 (6.8)	11 (12.8)	41 (17.6)	55 (15.2)
Deep vein thrombosis	0	0	4 (1.7)	4 (1.1)
Febrile neutropenia	0	1 (1.2)	2 (0.9)	3 (0.8)
Haematochezia	1 (2.3)	0	1 (0.4)	2 (0.6)
Tonsillitis	0	1 (1.2)	1 (0.4)	2 (0.6)
Pain in extremity	0	0	2 (0.9)	2 (0.6)
Pneumonia	0	0	2 (0.9)	2 (0.6)
Upper abdominal pain	0	0	2 (0.9)	2 (0.6)

Source data: [c31325825, Table B.5: 3]

The results of the DIVERSITY study (1160.106) conducted in 267 children from birth to <18years of age showed that DE was non-inferior to Standard of Care for thrombus resolution, and VTE recurrency with similar bleeding rates [P20-07911]. DE showed a favourable safety profile for prevention of recurrent VTE in children aged from >3 months to <18 years with persistent VTE clinical risk factor(s) evaluated in a long-term secondary VTE prevention study [P19-11322]. Overall, the DE clinical programme for paediatric patients showed an acceptable benefit-risk ratio and supports treatment of VTE and prevention of recurrent VTE in children from birth to <18 years.

However, limited evidence is available in early age children (from birth to <2 years) for treatment of VTE and prevention of recurrent VTE. This age group also showed the most marked differences from adults in haemostaseology [R15-4967]. The results of acute VTE treatment in this age group were evaluated in 35 cases of the DIVERSITY study (1160.106), where 22 patients received DE and 13 received Standard of Care [P20-07911]. The long-term secondary VTE prevention study (1160.108) evaluated 9 children at this early age group [c29754273-01].

The limited number of neonates and infants evaluated in the DE paediatric programme was connected with multiple challenges, including the relatively rare condition, a critically ill population with life threatening comorbidities, use of aggressive treatments, limited blood volumes that can be drawn for study purposes and, finally, parental consent that is often difficult to obtain in young children with acute serious conditions [R11-4524, P17-11774, P19-00949, R20-3318]. Thus, post-authorisation data collection was planned to characterize the safety profile of dabigatran in children under 2 years of age.

Completion of the PASS 1160-0307, a study to evaluate the safety of pediatric patients under 2 years of age receiving Pradaxa for the treatment of acute VTE treatment and prevention of recurrent VTE in

a routine clinical practice setting, did not provide any new safety information. The study was stopped at the end of the pre-defined enrolment period due to feasibility reasons, without any patients enrolled.

Boehringer has provided regular updates of post-marketing data through the PBRERs. To identify cases that might indicate patients aged 0 to 2 years who were born prematurely, Boehringer´s Global Safety Platform (BI GSP) was searched for cases reporting the term 'Premature baby' as an event or in the medical history of patients with age reported as being between 0 and 2 years. Between 11 Jan 2021 (EMA approval of the pediatric indication for Pradaxa) and the last PBRER with DLP 18 Mar 2025, no spontaneous case following the search criteria has been identified (Data sources: NW_AR-CMR-057 12 case bornpre (2025 03 18)).
In conclusion, safety data from the Pradaxa paediatric clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. Similarly, no relevant differences in the safety profile amongst age groups were apparent. No data exists concerning children 0 to 2 years of age who were born prematurely. However, no significant difference is expected.

Rationale for removal
Following the complete deregistration of the Pradaxa oral solution formulation in the countries where it was registered (EU countries in December 2023 with procedure no. EMEA/H/C/000829/II/0147/G, and Great Britain in May 2024), Boehringer Ingelheim considers that it will be unlikely that a significant number of children between 0-2 years of age who are able to swallow soft food, especially premature ones, will be treated with Pradaxa, taking into account the results of PASS 1160-307, the existence of suitable alternative in the market (rivaroxaban, oral solution), the overall low incidence of VTE in pediatric patients, and the absence of post-marketing data for this specific subpopulation.
Furthermore, the Pradaxa paediatric clinical development programme is complete, and Boehringer Ingelheim is not planning any further studies in this specific subpopulation.
Safety data from the Pradaxa clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. No data exists concerning children 0 to 2 years of age who were born prematurely. However, no significant difference is expected.
Based on this, Boehringer considers that there is no need to keep "Patients aged 0 to 2 years who were born prematurely" as missing information and proposes that this risk is removed from the list of Safety Concerns of the Risk Management Plan.

In the RMP update submitted with this response to RSI (RMP version 42.0), the missing information "Patients aged 0 to 2 years who were born prematurely" was proposed for removal in Section SVII.2. Related changes were done to the RMP in modules SIV, SVII, and SVIII, in Part V, and Part VI.

Boehringer will continue to monitor the safety of patients, including this subpopulation, through routine pharmacovigilance activities.

Assessment of the MAH's response

The MAH proposes the removal of the missing information "Patients aged 0 to 2 years who were born prematurely". The MAH's justification is acknowledged. Following the deregistration of the oral solution formulation, exposure in this population is expected to be negligible. This is supported by the experience from the paediatric PASS in which no patient could be enrolled and a search of the MAH's safety database in which no spontaneous case in this population could be identified. In addition, the data from clinical trials and post-marketing experience have not shown evidence of significant differences in the safety profile between children and adults. There are no risk management activities such as additional PhV activities to gain further knowledge, nor additional risk minimisation measures or routine risk minimisation activities recommending specific clinical measures, which would warrant maintaining this MI in the RMP.

The PRAC Rapporteur agrees that the missing information "Patients aged 0 to 2 years who were born prematurely" can be removed from the RMP.

Conclusion

Issue considered resolved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance