24 February 2022
EMA/202992/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Edarbi

International non-proprietary name: azilsartan medoxomil

Procedure No. EMEA/H/C/002293/II/0030/G

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	11 Oct 2021	11 Oct 2021	☐
☐	CHMP Rapporteur Assessment Report	15 Nov 2021	15 Nov 2021	☐
☐	CHMP members comments	29 Nov 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	02 Dec 2021	n/a	☐
☐	Start of written procedure	07 Dec 2021	07 Dec 2021	☐
☐	Request for Supplementary Information	09 Dec 2021	09 Dec 2021	☐
☐	Submission of Responses	25 Jan 2022	20 Jan 2022	
☐	Re-Start of procedure	26 Jan 2022	26 Jan 2022	☐
☐	CHMP Rapporteur Assessment Report	09 Feb 2022	31 Jan 2022	☐
☐	CHMP members comments	14 Feb 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	17 Feb 2022	22 Feb 2022	☐
☐	Start of written procedure	22 Feb 2022	n/a	☐
☒	Opinion	24 Feb 2022	24 Feb 2022	☐

Procedure resources	
Rapporteur:	Johann Lodewijk Hillege

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1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 20 September 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB
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Group of variations:

· Type II C.I.4. - Update of SmPC sections 4.2, 4.8 and 5.1 with paediatric clinical data from Study AR14.001 (PIP study 8) following the outcome of procedure EMEA/H/C/002293/P46/012.
· Type II C.I.4. - Update of SmPC section 5.2 with paediatric clinical data from Study TAK-491_109 (PIP study 7) following the outcome of procedure EMEA/H/C/002293/P46/011.
· Type II C.I.4. - Update of SmPC section 5.3 with data from juvenile animal toxicity studies.
· Type II C.I.4. - Update of SmPC section 4.5 with drug-drug interaction information from clinical pharmacology studies TAK-491-013 and TAK-563-004.

Furthermore, the MAH is taking the opportunity to update the PI in line with the latest QRD template version 10.2, update the local representatives for Ireland, Slovenia and United Kingdom in the Package Leaflet (PL) and update minor editorial/typographical to Product information.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

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

Current variation is submitted to update the product information (PI) for Edarbi with (1) relevant paediatric clinical data from Phase 1 study TAK-491_109 following the outcome of procedure EMEA/H/C/002293/P46/011 and Phase 3 study AR14.001 following the outcome of procedure EMEA/H/C/002293/P46/012; (2) data from 2 drug interaction studies TAK-491-013 and TAK-536-004 conducted in healthy adults; (3) data from juvenile animal toxicity studies.

(1) Two paediatric studies TAK491_109 and AR14.001 were previously assessed in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended, for Edarbi (EMEA/H/C/002293/P46/012 and EMEA/H/C/002293/P46/011). Both TAK-491_109 and AR14.001 showed consistent PK results. It was shown that the PK of azilsartan medoxamil is linear and similar to the PK in adults when allometric scaling is applied. Dosing in children should be performed based on body weight. The proposed update SmPC **section 5.2** to describe the paediatric PK data was not informative. The Applicant has been asked to mention that exposure of azilsartan is dependent on body weight and a comparison to adult data should be made. Preferably, simulated exposure data for typical patients with bodyweight of 25 kg and 50 kg should be presented at the studied doses.

In the Phase 3 paediatric study AR14.001, 10 mg tablet was used as a starting (in all subjects) or as a maintenance dose (in some subjects). 10 mg tablets are not commercially available yet and cannot be achieved by current authorised (adult) tablets of 20, 40 or 80 mg as no score line to accommodate dosing of 10 mg is available. Therefore, no dosing recommendations for children can currently be given, and the proposed text in **section 4.2** with a cross-reference to sections 5.1 and 5.2 for dosing used in the clinical studies can be agreed upon. Of note, the Applicant previously clarified that as soon as clinical Study AR14.002 (children 2 years or older with a body weight of less than 25 kg with primary or secondary hypertension) is completed, a request for authorisation of the age-appropriate sachets for oral suspension (10mg) as developed according to PIP Obligation and a paediatric indication will be considered. In general, the development of 10 mg sachets is highly encouraged to accommodate the dose recommendations and facilitate up titrations also for the higher age groups. Further, the application for a paediatric indication is highly encouraged as well.
Results from Study AR14.001 demonstrated that 6 weeks of daily treatment with azilsartan medoxomil (TAK-491) was sufficient to establish a steady state with notable changes in blood Section 4.5 is updated with drug interaction dataCompared with losartan, azilsartan medoxomil demonstrated a greater change in mean seated diastolic blood pressure from baseline to Week 6. A long term effect of AZM could be achieved on BP targets over 52 weeks of treatment during the open-label phase. It is supported to describe these data in **section 5.1**.
Further, no new safety concerns specific to this paediatric study population arose, and the overall safety profile of azilsartan medoxomil in the paediatric population was consistent with the known safety profile of azilsartan medoxomil in adults. Update to **section 4.8** to reflect these data is supported.

(2) Two drug interaction studies (Study TAK-491_013 and TAK-563-004) were previously submitted and assessed as part of the initial marketing authorisation of Edarbi (Azilsartan Medoxomil) (procedure EMEA/H/C/002293). No interaction has been observed with any of the investigated probe drugs. Administration of TAK491 and the drug combination (cocktail) did not have a clinically relevant effect on any of the tested cytochrome P450 enzymes; the exposure to the P-glycoprotein (P-gp) probe substrate was slightly decreased but is unlikely to be of clinical relevance. The proposed update SmPC **section 4.5** appropriately reflects the results of studies TAK-491_013 and TAK-563-004 and is in line with the text already included in the EPAR.

(3) Data from juvenile animal toxicity studies showed that juvenile rats seem to be more susceptible to angiotensin related altered renal morphology and function when exposed from postnatal week 2, which corresponds with the period of growth and maturation of the renal system. Species differences in renal development between rats and humans should be considered when interpreting the effects of ARBs in juvenile rats relative to human safety. The growth and maturation stage of the human renal system extends to about 2 years of age. Update to section 5.3 to reflect these data is supported.

Overall, proposed changes to sections 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 can be agreed upon. benefit-risk balance of Edarbi remains positive.

3. Recommendations

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

Variations requested		**Type**	**Annexes affected**
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Furthermore, the MAH is taking the opportunity to update the PI in line with the latest QRD template version 10.2, update the local representatives for Ireland, Slovenia and United Kingdom in the Package Leaflet (PL) and update minor editorial/typographical to Product information.

☒is recommended for approval.

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Changes have been made to section 4.2, 4.8 and 5.1 based on the Phase 3 paediatric study AR14.001 to reflect that no dosing recommendations for children can currently be given. The results from the study are reflected in section 4.8 and 5.1. Based on study TAK-491_109 an update is made to section 5.2 regarding PK data. Section 4.5 is updated with drug interaction data from studies TAK-491_013 and TAK-563-004 and section 5.3 is updated with data from juvenile animal toxicity studies.

SmPC new text

For more information, please refer to the Summary of Product Characteristics.

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

5. Introduction

Edarbi (Azilsartan medoxomil or TAK-491) is currently indicated for the treatment of essential hypertension in adults. TAK-491 is a prodrug that is rapidly hydrolysed to the active moiety, TAK-536, which is a potent and selective AT1 receptor antagonist. The recommended starting dose in adults is 40 mg once daily. The dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose.

Edarbi is not indicated for use in children or adolescents under 18 years of age.

Within the current variation, the MAH proposes to describe currently available data in children or adolescents 6 to < 18 years in sections 4.2, 4.8, 5.1, and 5.2. Further, an update of section 5.3 with data from juvenile animal toxicity studies is proposed; and an update of section 4.5 with data from drug interaction studies is proposed.

6. Non Clinical aspects

Azilsartan (TAK-536) is an angiotensin II receptor antagonist used in the treatment of hypertension. It is marketed in tablet form under the brand name Edarbi as the prodrug azilsartan medoxomil (TAK-491). The Applicant updated the SmPC section 5.3 with data from juvenile animal toxicity studies, which support the paediatric clinical studies.

Two-Week Toxicity Range Finding Study of TAK-491 and metabolite TAK-536 M-II in Juvenile Rats with a 4-Week Recovery Period, Oral Gavage, Report Number TAK-491-17050

This study was performed to evaluate the potential toxicity of TAK-491 and TAK-536 M-II (a major metabolite in humans) and its reversibility when administered to juvenile rats and to obtain data for dose setting for a subsequent definitive toxicity study in juvenile rats. A combination of TAK-491 and TAK-536 M-II was administered orally by gavage to juvenile Crl:CD(SD) rats at dosage levels of 0/0 (0.5% [w/v] MC containing 0.5% [w/v] citric acid), 1/2000, 10/2000, and 100/2000 mg/kg/day (expressed as TAK-491/TAK-536 M-II) for 2 weeks from Day 14 to Day 27 after birth.

Evaluation for TAK-491/TAK-536 M-II-related effects included clinical observations, body weight, hematology, blood chemistry, selected organ weights, gross pathology, and histopathology of the heart and kidney. In a dose range-finding study for effects of TAK-491 on heart development in neonatal rats (TAK-491-10810; dosage levels: 200 and 1000 mg/kg/day, dosing for 7 days to 0- and 7-day old animals), dilatation of the renal tubule was observed in all treated groups, and death and suppression of body weight gain were observed dose-dependently. These changes were slighter in the 7-day old animal group than in the 0-day old animal group. In the present study, dosing was initiated in 14-day old animals, 1 week later than in previous studies, and it was assumed that the onset of renal lesions was unlikely.

Accordingly, 100/2000 mg/kg/day was selected as the high dosage level, which was the middle dosage level in Study No. 08-339/su, and 10/2000 and 1/2000 mg/kg/day were selected as the middle and low dosage levels, respectively, in the present study. In the 100/2000 mg/kg group, 1 male died on Day 24 after birth (Day 10 of dosing) after observations of a decrease in spontaneous activity, prone position, emaciation, and a marked decrease in body weight. In the surviving animals, white stool and decreased body weight were noted after weaning and during the dosing period, respectively, in all treated groups. During the recovery, there was no significant difference in body weight in any treated group compared with 0/0, except in males in the 100/2000 mg/kg/day group on Day 31, suggesting reversibility.

At necropsy, no abnormal changes were noted in any group, including the animal that died. At the end of the dosing period, low kidney and heart weights were noted in all treated groups. At the end of the 4-week recovery period, increased kidney weight in females at ≥10/2000 mg/kg/day and increased heart weight in females at 100/2000 mg/kg/day were noted. In histopathology, tubular basophilia in the kidneys was observed in all treated groups at the end of the dosing period. At the end of the 4-week recovery period, tubular basophilia and/or thickening of the glomerular basal lamina, hyaline cast, hyaline droplets in the glomerulus in males, and/or mineralization at the cortico-medullary junction in females were observed in all treated groups. These changes were considered to have remained and/or to have arisen anew during the 4-week recovery period, but tubular basophilia in the kidney was considered to be on the verge of restoration after 4-week cessation of dosing since a similar lesion was observed in the control group to the same degree as in the treated groups.

Except for the persistence or new appearance of renal findings at the end of the 4-week recovery period, the findings from this study are similar to those seen in adult rat toxicity studies with TAK-491 or TAK-536 and are considered to reflect the exaggerated pharmacological effects of TAK-536 as an ARB (angiotensin II receptor blocker) when administered at high doses to normotensive rats.

From these results, it was concluded that the NOAEL of TAK-491/TAK-536 M-II for juvenile rats was less than 1/2000 mg/kg/day. Tubular basophilia in the kidney was considered to be reversible, although additional renal findings appeared during a 4-week recovery period.

Two-Week Range-Finding Toxicity Study of TAK-491 and TAK-536 M-II in 2 Weeks Old Rats, Oral Gavage, Report Number TAK-491-17075

TAK-491 at 0.01, 0.1, and 1 mg/kg/day, TAK-536 M-II at 200 and 2000 mg/kg/day, and 0.5% (w/v) MC solution containing 0.5% (w/v) citric acid were administered orally by gavage to Crl:CD(SD) rats for 2 weeks, from PND 14 to PND 27. Systemic exposures to TAK-536 and TAK-536 M-II were also assessed.

The doses for this studies were based on the results of TAK-491-17050 (see above), which did not determine a NOAEL at the dosage levels of TAK-491/TAK-536 M-II: 1/2000, 10/2000, and 100/2000 mg/kg/day based on the observations of low body weight and white stool noted in all treated groups during the dosing period and low kidney weight and renal tubular basophilia noted at necropsy. Therefore, TAK-491 and TAK-536 M-II were administered to juvenile rats in this study, to identify which article was involved in the induction of the changes observed in Report TAK-491-17050, and to determine the dosage levels for a subsequent 2-week oral dose definitive study of TAK-491 and TAK-536 M-II in juvenile rats with a 4-week recovery period. Now, 1 mg/kg/day of TAK-491 was set as the high dosage level, and middle and low dose levels were set at 0.1 and 0.01 mg/kg/day, respectively. For TAK-536 M-II, 2000 mg/kg/day was set as the high dosage level and 200 mg/kg/day was set as low dosage level.

In this study no animals died in any group. In the TAK-491 groups, low food consumption was noted transiently in both sexes on PND 21, and low heart weight was noted in males upon necropsy at 1 mg/kg/day. In histopathology of the kidney, an increase in the incidence of tubular basophilia was observed in all males and females. No treatment-related changes were observed in any examination at 0.01 and 0.1 mg/kg/day.

In the TAK-536 M-II groups, white stool was observed at 2000 mg/kg/day, but this was considered due to the excretion of unabsorbed test article and not an adverse effect of the test article. No other treatment-related changes were observed in any groups. In the toxicokinetic analysis, the mean Cmax and AUC24 of TAK-536 increased more than dose proportionally on PND 14 (first dosing) and on PND

27 (repeated dosing). In the TAK-491 groups, TAK-536 M-II was not detected in plasma except in 1 male (TAK-491 1 mg/kg after repeated dosing) on PND 27 before dosing. The mean Cmax and AUC24 values of TAK-536 M-II increased less than dose proportionally on PND 14 and PND 27 and were lower on PND 27 than on PND 14. In a former 4-week oral gavage toxicity study of TAK-491 in adult rats [TAK-491-00127], Cmax and AUC24 of TAK-536 and TAK-536 M-II PND 14 (first dosing) had been the similar levels as those at the final dosing. Therefore, the differences in the toxicokinetic parameters between PND14 and PND 27 in the present juvenile study were considered due to age difference of 2 weeks and 4 weeks of age in rats. There was no sex difference in the toxicokinetic parameters.

The findings from this study are similar to those seen in adult rat toxicity studies and are considered to reflect the exaggerated pharmacological effects of TAK-536 as an ARB (angiotensin II receptor blocker) when administered at high doses to normotensive rats. From these results, it was concluded that the NOAELs for 2-week old rats were 0.1 mg/kg/day for TAK-491 and 2000 mg/kg/day for TAK-536 M-II.

Two-Week Toxicity Study of TAK-491 and TAK-536 M-II in 2 Weeks Old Rats with a 4-Week Recovery Period, Oral Gavage, Report Number TAK-491-18059 (GLP)

Sprague-Dawley juvenile rats were dosed from PND 14 to PND 27 by oral gavage with TAK-491 at 0.1, 0.5, and 10 mg/kg/day, TAK-536 M-II at 2000 mg/kg/day, or vehicle. Evaluations for test article-related effects included clinical signs, body weight, clinical chemistry, hematology, selected organ weights, necropsy, and histopathology.

No animals died in any group and dosing of TAK-536 M-II did not induce any toxic changes. In the TAK-536 M-II groups, white stool was observed at 2000 mg/kg/day, due to excretion of unabsorbed test article. Decreased body weight and food consumption were noted during the dosing period in both sexes in the TAK-491 0.5 and 10 mg/kg/day groups, and decreased body weight was also noted during the early recovery period in the TAK-491 10 mg/kg/day group.

In hematology analysis, leukocyte and lymphocyte counts were decreased in females in the TAK-491 0.5 and 10 mg/kg/day groups at the end of the dosing period. Erythrocyte count, Hgb concentration, and Hct values were decreased, and the reticulocyte ratio was increased in both sexes at TAK-491 10 mg/kg/day but were not toxicologically significant because the changes were considered to be related to the pharmacological effects of the test article as an ARB at a high dose level in normotensive animals. Platelet count in males in the TAK-491 10 mg/kg/day group and reticulocyte ratio in both sexes in the TAK-491 0.5 mg/kg/day group were increased but were not considered toxicologically significant because the degree of change was slight, no test article-related changes were observed in histopathology, and/or there was no dose dependency. After the 4-week recovery period, no test article-related changes were noted in either sex, indicating a complete recovery of the changes.

In clinical chemistry, BUN and creatinine were increased in both sexes at TAK-491 10 mg/kg/day at the end of the dosing period. In females, alkaline phosphatase and ALT levels were increased, and total protein and calcium were decreased. In the TAK-491 0.5 mg/kg/day group, creatinine was increased in males, and ALT, BUN, and creatinine were increased and calcium was decreased in females. Except for BUN and creatinine, the changes were not considered to be toxicologically significant. After the 4-week recovery period, no test article-related changes were noted in either sex, indicating a complete recovery of the changes.

At necropsy, no test article-related changes were observed in any test article-treated group at the end of the dosing or recovery periods. Crown-rump length in the TAK-491 0.5 and 10 mg/kg/day groups and femur and humerus length in the TAK-491 10 mg/kg/day group were shorter than the respective length for those in the control group at the end of the dosing period. These changes may be due to the

TAK-91-related growth retardation in juvenile rats. After the 4-week recovery period, no test article-related changes were noted in either sex, indicating a complete recovery of the crown-rump or bone length.

In organ weight, low kidney weight in males was noted in the TAK-491 0.5 and 10 mg/kg/day groups at the end of the dosing period. Low heart weight in the TAK-491 10 mg/kg/day group and liver weights in the TAK-491 0.5 and 10 mg/kg/day groups were noted in both sexes. The changes in the liver and heart were considered to be secondary changes due to growth suppression and not toxicologically significant. These changes were comparable to the control group after the 4-week recovery period.

In histopathology, renal tubular basophilia in both sexes in the TAK-491 0.5 and 10 mg/kg/day groups and edema of renal papilla in males in the TAK-491 10 mg/kg/day group were observed at the end of the dosing period. At the end of the 4-week recovery period, renal tubular basophilia in the TAK-491 10 mg/kg/day group was observed with an incidence and severity that was lower than that at the end of the dosing period, indicating a recovery or partial recovery of this finding. Very slight edema of the renal papilla was noted with a higher incidence after the 4-week recovery period compared to at the end of the dosing period, suggesting the absence of recovery for this lesion.

In toxicokinetics, the average Cmax and AUC24 values of all analytes for TAK-491 groups were increased dose-proportionally on PND 14 and PND 27. On PND 27, TAK-491F was not detected in any TAK-491 groups, and Cmax and AUC24 values of all analytes, except for TAK-536 M-I, were lower than those on PND 14, suggesting a difference in metabolic capability in rats between PND 14 and PND 27. Average Cmax and AUC24 values for TAK-536 M-I were comparable on PND 14 and PND 27. There was no sex difference in any toxicokinetic parameter.

Except for the continued presence of slight renal papilla edema at the end of the recovery period, the findings from this study are similar to those seen in adult rat toxicity studies and are considered to reflect the exaggerated pharmacological effects of TAK-536 as an ARB when administered at high doses to normotensive rats.

From these results, it was concluded that the NOAEL for TAK-491 in juvenile rats was 0.1 mg/kg/day. The renal tubular basophilia induced by treatment with TAK-491 was reversible, but the renal papilla edema had not reversed during the 4-week recovery period. TAK-536 M-II did not induce any toxic change.

13-Week Toxicity Study of TAK-491 plus TAK-536 M-II in 3 Week Old Rats with a 4-Week Recovery Period, Oral Gavage, Report Number TAK-491-20224 (GLP)

Sprague-Dawley rats (10/sex/group) were dosed with TAK-491/TAK-536 M-II at 0.1/1000, 0.5/1000 or 10/1000 mg/kg/day from PND 21 through PND 111. The vehicle control used was 0.5% (w/v) MC solution containing 0.5% (w/v) citric acid. Systemic exposures to TAK-491F and its metabolites (TAK-536, TAK-536 M-I, and TAK-536 M-II) were also assessed. Evaluations included clinical signs, body weight, food consumption, morphological development of the reproductive organs, hematology, clinical chemistry, organ weights, and histopathology of selected organs. Toxicokinetic analysis of TAK-491F, TAK-536, TAK-536 M-I, and TAK-536 M-II was conducted in satellite animals, after the first (PND 21; 18/sex/treated group) and last (PND 111; 4/sex/treated group) dose.

No animal died in any group. Decreased body weight and food consumption were noted during the dosing period and the recovery period in males and similar changes were noted during the early phase of the dosing period in females at 10/1000 mg/kg/day. These changes were not considered to be toxicologically significant, and they recovered after a 4-week cessation of dosing.

In hematology, erythrocyte count, Hgb concentration, and Hct value were decreased in both sexes at 10/1000 mg/kg/day at the end of the dosing period. These changes were considered to be related to the pharmacological effects of the test article as an ARB at a high dose level in normotensive animals, and were not considered to be toxicologically significant. In this group, decreased prothrombin time and activated partial thromboplastin time were noted in both sexes but were not considered to be toxicologically significant. After recovery, no test article-related changes were noted in either sex.

In clinical chemistry, BUN and creatinine were increased in both sexes at 10/1000 mg/kg/day at the end of the dosing period. Although these changes were considered to be related to the pharmacological effect of the test article, the increase in BUN accompanied by the increase in creatinine was an exaggerated effect, and was considered to be toxicologically significant. After recovery, a milder increase in BUN was seen in males at 10/1000 mg/kg/day. This change was not considered to be toxicologically significant.

In organ weights, decreased heart weight in both sexes and increased kidney weight in females were noted at 10/1000 mg/kg/day at the end of the dosing period; the increased kidney weight remained at the end of the recovery period and was considered adverse. Decreased heart weight is considered a class effect of ARBs in normotensive animals and is not considered to be toxicologically significant.

In histopathology on the kidney, tubular basophilia with or without infiltration of mononuclear cells was observed in both sexes at 10/1000 mg/kg/day at the end of the dosing period. These changes were considered to be toxicologically significant. In the 0.5/1000 and 10/1000 mg/kg/day groups, hypertrophy of the juxtaglomerular cell was observed in both sexes, but this change was considered to be related to the pharmacological action of the test article as an ARB, and not to be toxicologically significant. No test article-related histopathological lesions were noted in other tissues at the end of the dosing period. After the 4-week recovery period, tubular basophilia with or without infiltration of mononuclear cells and very slight hypertrophy of the juxtaglomerular cell were observed in both sexes at 10/1000 mg/kg/day. However, these renal findings at the end of the recovery period were reduced in incidence and severity when compared with those at the end of the dosing period, suggesting a partial recovery.

The toxicological profile noted in the present study was qualitatively similar to that in the previous 13-week study in 6-week-old rats [Report 491-00143-001A]. In both studies, no test article-related changes were observed in clinical signs, morphological differentiation of external genitalia, or in necropsy findings in either sex in any test article group.

Toxicokinetic analysis of plasma drug and metabolite levels conducted after the first and last dosing of TAK-491 indicated that TAK-491F was not detected in any animal except for 1 male at 0.5/1000 mg/kg/day. Mean Cmax and AUC24 values for TAK-536 and TAK-536 M-I increased with increasing doses of TAK-491 at both collection time periods, whereas Cmax and AUC24 values for TAK-536 M-II did not differ appreciably between dose groups. With repeated dosing, Cmax values for TAK-536 were relatively unchanged after the first and last dose except for values in females at 10/1000 mg/kg/day, whereas AUC24 values for TAK-536 were decreased in all groups at the end relative to the start of the dosing period. For TAK-536 M-I and TAK-536 M-II, mean Cmax and AUC24 values increased and decreased over time, respectively, in all groups. Time to reach Cmax (tmax) for TAK-536, TAK-536 M-I, and TAK-536 M-II tended to occur earlier with repeated dosing. There was no sex difference in any toxicokinetic parameter. The results of the toxicokinetic analysis are shown in Table 6.1.

Table 6.1: Toxicokinetics From a 13-Week Toxicity Study in 3-Week-Old Rats--AUC24 (Mean Values) on Day 0 and in Week 13:

		AUC24 (µg·hr/mL)					
		TAK-491/TAK-536 M-II					
		0.1/1000		0.5/1000		10/1000	
Analyte	Day	M	F	M	F	M	F
TAK-491F	0	0	0	0.007	0	0	0
	111	0	0	0	0	0	0
TAK-536	0	2.635	2.388	14.350	15.662	381.096	432.811
	111	1.731	1.391	10.123	10.699	236.127	274.345
TAK-536 M-I	0	0	0	0.026	0.032	1.484	1.663
	111	0.027	0.014	0.447	0.302	6.665	8.842
TAK-536 M-II	0	264.787	195.237	198.101	218.343	365.697	372.884
	111	65.669	40.080	61.989	52.008	63.824	59.447

Source: TAK-491-20224.

AUC_{24}: area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}: maximum observed plasma concentration; F: female(s), M: male(s); NC: not calculated; t_{max}: time of first occurrence of C_{max}.

Based on the results of the current study, it was concluded that the NOAEL was 0.5/1000 mg/kg/day. After a 4-week recovery period there was a trend for recovery of all test article-related changes, except for the effects on kidney weights at 10/1000 mg/kg/day.

Assessor's comment:

Two-week oral gavage dose range-finding studies in 2-week-old juvenile rats were performed to evaluate the potential toxicity of TAK-491 and the major metabolite in humans TAK-536 M-II for the selection of appropriate dosages for a definitive study. Except for the persistence or new appearance of renal findings, the findings were similar to those seen in adult rat toxicity studies with TAK-491 or TAK-536 and are considered to reflect the exaggerated pharmacological effects of TAK-536 as an angiotensin II receptor blocker (ARB) when administered at high doses to normotensive rats.

In the definitive repeat dosing study of TAK-491 and TAK-536 M-II in 2-week-old juvenile rats for two weeks with a 4-week recovery period, the NOAEL for TAK-491 was found 0.1 mg/kg/day. Except for the continued presence of slight renal papilla oedema at the end of the recovery period, the findings from this study are similar to those seen in adult rat toxicity studies and are considered to reflect the exaggerated pharmacological effects of TAK-536. The renal tubular basophilia induced by treatment with TAK-491 was reversible. TAK-536 M-II did not induce any toxic change at 2000 mg/kg/day. In a 13-week repeat oral dosing study in 3-week-old juvenile rats with TAK-491/TAK-536, it was shown that the NOAEL was 0.5/1000 mg/kg/day. After a 4-week recovery period, there was a trend for recovery of all test article-related changes, except for the effects on kidney weights at 10/1000 mg/kg/day. The toxicological profile was qualitatively similar to that in the previous 13-week study in 6-week-old rats. No test article related changes were observed in clinical signs, morphological differentiation of external genitalia, or necropsy findings in either sex in any test article group.

These results show that juvenile rats seem to be more susceptible to angiotensin-related altered renal morphology and function when exposed from postnatal week 2, which corresponds with the renal system's period of growth and maturation. Species differences in renal development between rats and humans should be considered when interpreting the effects of ARBs in juvenile rats relative to human safety. The growth and maturation stage of the human renal system extends to about 2 years of age.

The Applicant added this new information on juvenile oral toxicity in SmPC 5.3. However, the text is not in good order and should be amended (see **9.6 Update of the Product Information**).

7. Clinical aspects

Of note, all studies were previously assessed. Study TAK-491_013 and TAK-563-004 were submitted as part of the initial marketing authorisation of Edarbi (Azilsartan Medoxomil) (procedure EMEA/H/C/002293). Study AR14.001 was submitted during the Article 46 of Regulation (EC) No. 1901/2006 procedure for Edarbi (EMEA/H/C/002293/P46/012.1). Study TAK-491_109 was submitted in paediatric worksharing Article 46 procedure EMEA/H/C/002293/P46/011. Therefore, only a short overview of the study design and results will be presented here.

Study AR14.001

Study AR14.001 is a global, phase 3, randomised, double-blind study of the efficacy and safety of AZM in children 6 to <18 years of age with primary or secondary hypertension.

At 67 sites, a total of 215 subjects participated in a 6-week, double-blind, randomised, treatment phase (DB phase), followed by a 2-week, double-blind, randomised placebo-controlled withdrawal phase (WD phase). In the DB phase, subjects were randomized (1:1:1:1) to the following groups: AZM-L (low-dose AZM [10 mg]), AZM-M (intermediate-dose AZM [20 mg]), and AZM-H (high-dose AZM [40 mg/80 mg]), or losartan.

In the WD phase, subjects were randomised (1:1) to continue taking their previously assigned active treatment or were switched to placebo. This study also included a 44-week, open-label extension (OL phase), in which all subjects received AZM (AZM only subset) or AZM and other antihypertensive medications as needed (AZM plus subset) in a titrate to-target blood pressure (BP) dosing algorithm.

During 52 weeks AZM tablets or placebo tablets were administered once a day orally in the dose mentioned in Table 1.

The doses selected in AR14.001 were based on the PK modelling and simulation of data from Study TAK-491_109 in paediatric subjects (aged 6 to <17 years) that indicated that the 20, 40, and 80 mg doses of azilsartan medoxomil, each of which was demonstrated to be safe and effective in phase 3 studies of hypertensive adult subjects, provided similar levels of exposure in children who weighed 50 to 100 kg as had been observed in adults. A dose range that included the 10, 20, and 40 mg strengths of azilsartan medoxomil was administered to lower-weight subjects (ie, 25 to <50 kg) to maintain similar exposures in those children as was observed at the 20 to 80 mg doses in adults.

Table 1. Daily dose of AZM or placebo

Treatment	Body Weight	Double-Blind Phase		Withdrawal Phase
		Weeks 0-2	Weeks 2-6	Weeks 6-8
AZM-L	≥25 to <50 kg	10 mg	10 mg	10 mg or placebo
	≥50 kg	10 mg	10 mg	10 mg or placebo
AZM-M	≥25 to <50 kg	10 mg	20 mg	20 mg or placebo
	≥50 kg	10 mg	20 mg	20 mg or placebo
AZM-H	≥25 to <50 kg	10 mg	40 mg	40 mg or placebo
	≥50 kg	10 mg	80 mg	80 mg or placebo
Open-Label Phase				
Body Weight	Weeks 8-12		Weeks 12-52	
≥25 to <50 kg	AZM 10 mg		AZM 10, 20, or 40 mg	
≥50 kg	AZM 10 mg		AZM 10, 20, 40, or 80 mg	

The primary objective was to evaluate the antihypertensive effect of azilsartan medoxomil compared with placebo after a randomized, double-blind withdrawal. Hypertension was defined as clinic seated diastolic blood pressure (seDBP) ≥95th percentile (by age, gender, and height) or ≥90th percentile (by age, gender, height) if chronic renal disease, diabetes, heart failure, or hypertensive target-organ damage was present. Secondary objectives included evaluation of the antihypertensive effect of azilsartan medoxomil compared with losartan during double-blind treatment, and evaluation of the safety and tolerability of azilsartan medoxomil compared with placebo and losartan during double-blind treatment and of azilsartan medoxomil during a longterm, open-label extension. An additional objective was the assessment of the population PK of azilsartan (TAK-536), the active moiety of azilsartan medoxomil (please see the summary of the PK data further below).

Overall Efficacy Conclusions

The primary objective of Study AR14.001—to evaluate the antihypertensive effect of azilsartan medoxomil compared with placebo after a randomized, double-blind, withdrawal (WD Phase)— was met by using an analysis of covariance (ANCOVA) of the primary endpoint (change from Week 6/Final Visit of the DB Phase to Week 8/Final Visit of the WD Phase in mean seDBP between azilsartan medoxomil [pooled] and placebo). The following conclusions regarding study efficacy directly support the proposed updates to the Edarbi label.

The primary analysis demonstrated the following:

- Six weeks of treatment with azilsartan medoxomil was sufficient to establish steady state with notable changes in blood pressure; a 2-week withdrawal with placebo was sufficient to detect a loss of blood pressure control in subjects randomized to placebo, whereas those subjects who remained on azilsartan medoxomil treatment had stable blood pressure control. The difference in mean seDBP change from Week 6 to Week 8 in the subjects treated with azilsartan medoxomil versus placebo was -5.42 mmHg (95% CI, -7.29 to -3.55 mmHg; $p < 0.001$).

Analyses of secondary efficacy endpoints demonstrated the following:

- Study subjects treated with azilsartan medoxomil had a statistically significant greater change in mean seDBP from baseline to Week 6 compared with losartan-treated subjects; the difference in mean seDBP change was -3.48 mmHg (95% CI= -6.17 to -0.78 mmHg; p = 0.012) for azilsartan medoxomil versus losartan.
- Percentage of subjects who achieved target blood pressure (seDBP, seSBP, both) with the target defined as <90th percentile for age, gender, and height at Week 8 was significantly higher after azilsartan medoxomil treatment compared with placebo; 54.5% of azilsartan medoxomil-treated subjects and 30.4% of subjects receiving placebo achieved target blood pressure (p = 0.005).

Additional exploratory dose-response analysis conducted by using linear regression models with weight-adjusted dose (mg/kg) as a covariate did not show a dose-dependent effect on change from baseline to Week 6 (ie, end of the DB Phase) in clinic seDBP, seSBP, or MAP in the dose range tested.

In conclusion, azilsartan medoxomil is superior to placebo in the treatment of hypertension in children aged 6 to <18 years in that it demonstrated statistically significant and clinically relevant improvements of efficacy variables measured in this study. Azilsartan medoxomil provided clinical improvement in the treatment of hypertension in children aged 6 to <18 years compared with losartan during the randomized, double-blind treatment and withdrawal, as well as the open-label extension of this study.

Overall Safety Conclusions

In the 6-week DB Phase, 162 subjects were exposed to azilsartan medoxomil, and 53 were exposed to losartan. In the 2-week WD Phase, 77 subjects were exposed to azilsartan medoxomil, 103 were exposed to placebo, and 23 were exposed to losartan. In the 44-week OL Phase, 156 subjects were exposed to azilsartan medoxomil alone (AZM Only), and 41 subjects were exposed to azilsartan medoxomil and other antihypertensives (AZM Plus).

There were no notable differences in duration of exposure between groups in the DB and WD Phases of the study. In the DB Phase, subjects were taking the drug for a mean of 41.9 and 40.1 days in the pooled azilsartan medoxomil and losartan groups, respectively. In the WD Phase, subjects were taking the study drug for a mean of 14.9, 14.6, and 14.3 days in the pooled azilsartan medoxomil, losartan, and placebo groups, respectively. In the OL Phase, subjects were taking the drug for a mean of 290.8 and 309.8 days in the AZM Only and AZM Plus subsets, respectively.

DB period

The overall percentage of subjects experiencing TEAEs (including nonserious and serious) were similar in the pooled AZM group and losartan group (33.3% and 32.1%, respectively). Most TEAEs were unrelated to the study drug. A small percentage of subjects (5.6%) experienced TEAEs related to AZM; no TEAEs were related to losartan. The most frequently reported primary SOCs were infections and infestations (16.0% in the AZM group; 11.3% in the losartan group) and nervous system disorders (8.0% in the AZM group; 9.4% in the losartan group). Most TEAEs in the DB phase were mild. Moderate TEAEs were reported in 13 (8.0%) subjects in the pooled AZM group and in 4 (7.5%) subjects in the losartan group. Severe TEAEs were uncommon; 1 (0.6%) subject in the pooled AZM group and 1 (1.9%) subject in the losartan group. Three subjects were discontinued from the DB phase due to TEAEs (2 serious events [loss of consciousness and hypertension] and 1 nonserious event [presyncope]); 2 (3.8%) of these subjects were taking losartan, and 1 (1.8%) subject was taking AZM-M. In the DB phase, occurrence of serious TEAEs was low and identical between the 2 drug

groups; serious TEAEs were reported in 2 (1.2%) subjects in the pooled AZM group and in 2 (3.8%) subjects in the losartan group. None of the serious TEAEs were related to AZM or losartan.

WD phase

The rate of subjects experiencing TEAEs (including nonserious and serious) was higher in the pooled AZM group compared with the placebo and losartan groups (15.6%, 12.6%, and 8.7% of subjects, respectively. Most TEAEs in the WD phase were unrelated to the study drug. Small percentages of subjects reported TEAEs related to AZM (2.6% of subjects) and related to placebo (2.9% of subjects). There were no TEAEs related to losartan. The most frequently reported primary SOCs were infections and infestations (6.5% in the AZM group; 8.7% in the losartan group; 2.9% in the placebo group) and nervous system disorders (3.9% in the AZM group; 5.8% in the placebo group; none in the losartan group). Most TEAEs in the WD phase were mild (7 [9.1%] in the pooled AZM group, 11 [10.7%] in the placebo group, and 2 [8.7%] in the losartan group). Moderate TEAEs were reported in 4 (5.2%) subjects taking AZM, in 2 (1.9%) subjects taking placebo, and in none of the subjects taking losartan. There was 1 (0.6%) subject with a severe TEAE in the WD phase; this subject was taking AZM. There was 1 (1.3%) subject with a serious TEAE (upper respiratory tract infection) in the WD phase; this subject was taking AZM, but the event was deemed unrelated to the drug. None of the subjects taking placebo or losartan experienced serious TEAEs. No subjects were discontinued due to serious or nonserious TEAEs in the WD or OL phases.

OL phase

The proportion of subjects experiencing TEAEs in the AZM plus subset was higher (82.9%) compared with the AZM only subset (32.7%). The incidence of treatment-related TEAEs was also higher in the AZM plus subset (14.6%) compared with the AZM only subset (2.6%). Severe TEAEs were reported for 1.9% and 7.3% of subjects in the AZM only and AZM plus subsets, respectively. A similar proportion of subjects in both subsets experienced serious TEAEs (4.5% in the AZM only subset and 4.9% in the AZM plus subset). None of the serious TEAEs were related to the study treatment. The most frequently reported primary SOCs were infections and infestations (15.4% and 63.4% in the AZM only and AZM plus subsets, respectively); Gastrointestinal disorders (10.9% and 22.0% in the AZM only and AZM plus subsets, respectively); and nervous system disorders (9.0% and 17.1% in the AZM only and AZM plus subsets, respectively).

SAE & death

The incidence of serious TEAEs in the DB, WD, and OL phases was low and similar between drug groups (ie, AZM vs losartan vs placebo; AZM only vs AZM plus). There were no deaths in the DB, WD, or OL phases of this study.

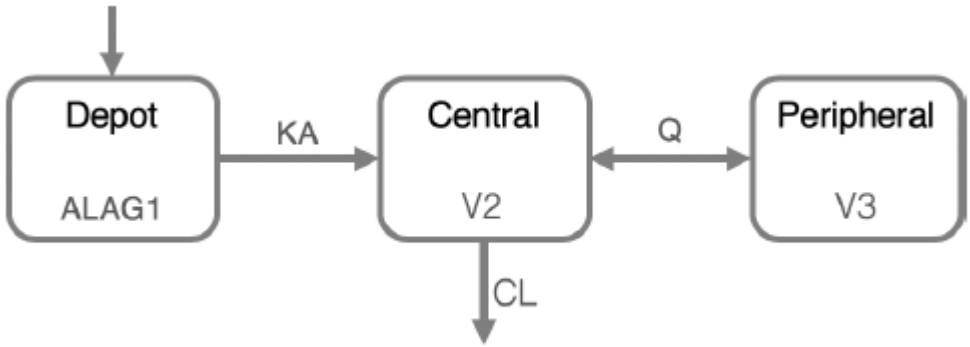
In summary, treatment with AZM-L, AZM-M, and AZM-H (20 to 80 mg) was safe and tolerable compared with placebo and losartan in the treatment of paediatric hypertension in children aged 6 to <18 years after a randomized, double-blind treatment and withdrawal, as well as an open-label extension with azilsartan medoxomil alone or in combination with other antihypertensives in this study. The overall safety profile of azilsartan medoxomil in the paediatric population was consistent with the known safety profile in adults.

PK data from study AR14.001

In clinical study AR14.001 the population PK of the active metabolite azilsartan (TAK-536) was evaluated as an additional objective. In this study, azilsartan medoxomil in a dose of 10 mg to a maximum of 80 mg was administered for 6 weeks, and sparse PK samples were collected. Subjects

with a bodyweight of ≥25 to <50 kg could receive a dose of 10-40 mg and subjects with a bodyweight of ≥50kg could receive a dose of 10-80mg. The dataset of the population PK model contained 988 records from 162 subjects enrolled in study AR14.001. Only children aged 6 years and older were included. The population PK model used, was based on the previous model developed in Study TAK-491109. The PK model structure is described in the figure below.

Figure 1. Schematic of the final population PK model structure



The final study AR14.001 model is very similar to the 109 model except that the residual variability was estimated as 37.8%, which was larger than the original estimate (25.5%). Weight on CL and weight on V2 were relevant parameters in the final model. Allometric scaling was used to describe systemic clearance (CL) and the central compartment (V2), see population parameter estimates below.

Table 2. Final parameter estimates of the final; AR14.001 model

	Final Parameter Estimate		Between Subject Variability /Residual Variability	
Parameter	**Typical Value**	**RSE%**	**Typical Value as CV%**	**RSE%**
CL (L/h)	1.00	fixed	34.1	fixed
V2 (L)	5.69	fixed	40.7	fixed
KA (1/h)	1.13	fixed	0	fixed
Q (L/h)	0.591	fixed	0	fixed
V3 (L)	15.5	fixed	0	fixed
WEIGHT on CL	0.763	fixed		
WEIGHT on V2*	1.09	fixed		
Ratio of Additive to Proportional RV	480	fixed		
ALAG1 (h)	0.202	fixed	0	fixed
RV	0.143	7.3	37.8	

The table lists final parameter estimates and relative standard error in percent (RSE%) for both, typical parameters (fixed effects) and between subject variability parameters (random effects). Parameters were estimated on oral data only which is why above listed clearance and volume terms refer to apparent parameters, i.e., for example, CL denotes CL/F where F is the (not estimated) bioavailability.

Study TAK-491_109

Study TAK-491_109 was a comparative single-dose pharmacokinetic and safety study of azilsartan medoxomil (TAK-491) between infants, children, and adolescents with hypertension and healthy adults. The study has been conducted as a part of the pediatric clinical development program.

The clinical part of the study has been completed in July 2013, and the study report in March 2014. The study included:

- 9 pediatric subjects aged ⩾12 to <17 years and 9 adult subjects in Cohort 1,
- 8 pediatric subjects aged ⩾6 to <12 years in Cohort 2, and
- 3 pediatric subjects aged ⩾1 to <6 years in Cohort 3

For adult and pediatric subjects aged ≥6 to <17 years TAK-491 tablets (20 and 40 mg) were used, and for the pediatric subjects aged ≥1 to <6 years TAK-491 granules for reconstitution (10 mg per sachet) were used to administer a dose equivalent to TAK-491 0.66 mg/kg body weight.

The pharmacokinetics and urinary excretion data for the active metabolite azilsartan (TAK-536) and main inactive metabolite TAK-536 M-II were determined, and descriptive statistics were provided. Further, population PK modelling was performed and used to compare simulated exposures to TAK-536 in pediatric subjects and healthy adults.

Based on this study, it was concluded that PK data in children are comparable to the adult data and a single dose of azilsartan medoxomil was well tolerated in this study. The results of the PK data analysis indicate that the dose of azilsartan medoxomil should be adapted for children dependent on their body weight. Administration of the granules resulted in faster absorption than observed for the tablets, with a t_{max} of 1 hr for the granules and 2 hr for the tablets.

Study TAK-491-013

In study TAK-491_013 the interaction between TAK 491 and multiple cytochrome P450 (CYP) probe substrates was investigated. A cocktail of midazolam (3A4), caffeine (1A2), tolbutamide (2C9), dextromethorphan (2D6), and fexofenadine (P-gp substrate) was administered. TAK-491, administered as 80 mg for 5 days, did not have a clinically relevant effect (inhibition or induction) on any of the tested cytochrome P450 enzymes (3A4, 1A2, 2C9, 3A4 and 2D6). The exposure to fexofenadine (P-gp substrate) was decreased, 16% reduction in AUC from time 0 to infinity, and 27% reduction in C_{max}.

Study TAK-563-004

In supportive study TAK-536_004 the interaction between TAK 536 (azilsartan) and multiple cytochrome P450 (CYP) probe substrates was investigated, the design of the study was the same as study TAK-491_013. Co administration of TAK-536 and the drug cocktail did not have a clinically relevant effect on any of the tested cytochrome P450 probe substrates, the exposure to the P-gp substrate not affected.

8. PRAC advice

N/A

9. Changes to the Product Information

As a result of this group of variations, sections 4.2, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are being updated to reflect the data obtained from two paediatric studies TAK-491_109 (Study 7) and AR14.001 (Study 8), data from drug interaction studies (TAK-491-013 and TAK-536-004) and data from the juvenile animal toxicity studies. The Package Leaflet (PL) is updated accordingly.

In addition, the list of local representatives in the PL is being revised.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9.1 Update of SmPC section 4.2 based on the paediatric clinical data from Study AR14.001 (PIP study 8) following the outcome of procedure EMEA/H/C/002293/P46/012

Section 4.2

The MAH proposes to update SmPC section 4.2 with paediatric clinical data from Study TAK-491_109. The following changes are proposed (Deleted text: ~~strike trough~~, additions: **bold underlined**):

Posology

The recommended starting dose **in adults** is 40 mg once daily. The dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose.

…

Paediatric population

Edarbi is not indicated for use in children or adolescents under 18 years of age. Currently available data in children or adolescents 6 to < 18 years of age are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made. The safety and efficacy of Edarbi in children ~~and adolescents aged 0 to~~ < ~~18~~6 years **of age** have not yet been established.

No data are available.

CHMP Rapporteurs comment

The study AR14.001 has been evaluated in Article 46 of Regulation (EC) No. 1901/2006 procedure for Edarbi (EMEA/H/C/002293/P46/012.1). It was concluded that the data from the Study AR14.001 would support acceptance of an indication (and therefore dosing) for this specific paediatric population.

Based on the study AR14.001 results, as well as a previous PK study, it is clear that dosing in children should be performed based on body weight, with a starting dose of 10 mg.

However, 10 mg tablet used in the paediatric study AR14.001 is not commercially available yet and cannot be achieved by current authorised (adult) tablets of 20, 40 or 80 mg as no score line to accommodate dosing of 10 mg is available. Therefore, no dosing recommendations for children can currently be given and the proposed text in section 4.2 with a cross-reference to sections 5.1 and 5.2 for dosing used in the clinical studies can be agreed.

In the Article 46 of Regulation (EC) No. 1901/2006 procedure for Edarbi (EMEA/H/C/002293/P46/012.1), the Applicant clarified that as soon as clinical Study AR14.002 (children 2 years or older with a body weight of less than 25 kg with primary or secondary hypertension) is completed, request for authorisation of the age-appropriate sachets for oral suspension (10 mg) as developed according to PIP obligation will be considered. In general, the development of 10 mg sachets is highly encouraged to accommodate the dose recommendations and facilitate up titrations also for the higher age groups. Also, as indicated in the Article 46 procedure, the plans for a paediatric indication will be considered by the Applicant, as appropriate, once the clinical Study AR14.002 (children 2 years or older with a body weight of less than 25 kg with primary or secondary hypertension) is completed. The application for a paediatric indication is highly encouraged as well.

Conclusion

No dose recommendations for children 6 to <18 years of age can currently be given. Update to section 4.2 as proposed can be agreed.

9.2 Update of SmPC section 4.5 with drug-drug interaction information from clinical pharmacology studies TAK-491-013 and TAK-563-004.

The MAH proposes to update of SmPC section 4.5 with drug-drug interaction information from clinical pharmacology studies **TAK-491-013** and **TAK-563-004**.

The following changes are proposed (Deleted text: ~~strike trough~~, additions: **bold underlined**):

Additional information

Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

No clinically significant interactions have been reported in studies of azilsartan medoxomil or azilsartan given with amlodipine, antacids, chlortalidone, digoxin, fluconazole, glyburide, ketoconazole, metformin, and warfarin. **Following administration with a mixture of cytochrome P450 (CYP) probe substrates, no clinically significant drug interactions were observed with caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), or midazolam (CYP3A4).**

CHMP Rapporteurs comment

Study TAK-491_013 and TAK-563-004 were previously submitted and assessed as part of the initial marketing authorisation of Edarbi (Azilsartan Medoxomil) (EMEA/H/C/002293). The Applicant selected TAK-491 for development rather than TAK-536 as TAK-491 had a better pharmacokinetic profile, with a lower C_{max} and a t_{max} of approximately 3 hours. Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastrointestinal tract and/or during drug absorption. Studies with Azilsartan were regarded supportive (and especially less relevant for the assessment of gastrointestinal interactions).

The interaction between Azilsartan Medoxomil / Azilsartan and several cytochrome P450 probe substrates in a cocktail was investigated in Studies TAK-491_013 and TAK-563-004. As mentioned in the EPAR (https://www.ema.europa.eu/en/documents/assessment-report/edarbi-epar-public-assessment-report_en.pdf), no interaction has been observed with any of the investigated probe drugs. Administration of TAK-491 and the drug combination (cocktail) did not have a clinically relevant effect on any of the tested cytochrome P450 enzymes, the exposure to the P-glycoprotein (P-gp) probe substrate was slightly decreased. Probably this interaction is not clinically relevant, as no interaction with digoxin was observed in study TAK-491_104. The absence of the interaction with Pgp- probe digoxin is already mentioned in the SmPC.

The proposed update SmPC section 4.5 appropriately reflects the results of studies TAK-491_013 and TAK-563-004 and is in line with the text already included in the EPAR.

In EMA Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2**(2012) is mentioned that information on absence of interactions (supported by in vivo data) could be reported briefly if considered of interest to the prescriber and that results of interaction studies used to predict other drug-interactions on a mechanistic basis e.g. interaction studies with probe drugs as victim drugs, should be included, even if the interaction effect is not clinically relevant for the specific victim drug studied.

Conclusion

Update of SmPC section 4.5 with drug-drug interaction information on cytochrome P450 probes is considered acceptable.

9.3 Update of SmPC section 4.8 based on the paediatric clinical data from Study AR14.001 (PIP study 8) following the outcome of procedure EMEA/H/C/002293/P46/012

Section 4.8

The MAH proposes to update SmPC section 4.8 with paediatric safety information.
The following changes are proposed (Deleted text: ~~strike trough~~, additions: **bold underlined**):

Summary of the safety profile

Edarbi at doses of 20, 40 or 80 mg has been evaluated for safety in clinical studies **in adult** patients treated for up to 56 weeks.

…

Paediatric population

A clinical study on the safety and efficacy of Edarbi in children and adolescents 6 to < 18 years of age was conducted (see section 5.1). The overall safety profile of Edarbi in the paediatric population was consistent with the known safety profile in adults.

CHMP Rapporteurs comment

The safety data from the study AR14.001 was evaluated in detail during the Article 46 of Regulation (EC) No. 1901/2006 procedure for Edarbi (EMEA/H/C/002293/P46/012.1). In short, the clinical safety profile of Edarbi in children was considered acceptable and consistent with the known safety profile of the drug in adults. No new (serious) safety concerns were raised. It was, however, noted that out of 9 TEAEs in the AZM group during the DB phase that were considered by the investigator to be related to study treatment, 4 of them, i.e., headache, abdominal pain, back pain, and cough, are currently not mentioned in the registered SmPC of AZM. Since these AEs were non-serious and occurred only in one subject, no concern is raised. Nevertheless, any further detailing could be considered during a possible type II variation in the future when the data from another ongoing paediatric study (AR14.002) become available.

The proposed update to section 4.8 can be accepted.

Conclusion

Update of SmPC section 4.8 with the statement on the safety in the paediatric population is considered acceptable.

9.4 Update of SmPC section 5.1 with the paediatric clinical data from Study AR14.001 (PIP study 8) following the outcome of procedure EMEA/H/C/002293/P46/012.

Section 5.1

The MAH proposes to update SmPC section 5.1 with the data from paediatric Phase 3 study AR14.001.
The following changes are proposed (Deleted text: ~~strike trough~~, additions: **bold underlined**):

Paediatric population

~~The European Medicines Agency has deferred the obligation to submit the results of studies with Edarbi in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use).~~**The antihypertensive effects of azilsartan medoxomil were evaluated in a Phase 3 randomized, double blind study in children or adolescents 6 to < 18 years of age with primary or secondary hypertension. This study involved a 6 week, double blind, randomized treatment phase (DB Phase), followed by a 2 week, double blind, randomized placebo controlled withdrawal phase (WD Phase). In the DB Phase, subjects were**

randomized (1:1:1:1) to the following groups: azilsartan medoxomil 10 mg, 20 mg, and 40 mg/80 mg (based on subject body weight), or losartan. In the WD Phase, subjects were randomized (1:1) to continue taking their previously assigned active treatment or were switched to placebo. This study also included a 44 week, open label extension (OL Phase), in which all subjects received azilsartan medoxomil or azilsartan medoxomil and other antihypertensive medications as needed in a titrate to target blood pressure dosing algorithm.

In the 2 week withdrawal period, there was a loss of blood pressure control in subjects randomized to placebo, while subjects who remained on azilsartan medoxomil treatment had stable blood pressure control. Subjects who were treated with azilsartan medoxomil (all doses pooled) had a statistically significantly greater change in mean seated DBP from baseline to Week 6 compared with losartan-treated subjects. Percentage of subjects who achieved target blood pressure (defined as < 90th percentile for age, gender, and height) at Week 8 (week 2 of the withdrawal period) was significantly higher with azilsartan medoxomil treatment compared with placebo.

In the 6 week DB Phase, 162 subjects were exposed to azilsartan medoxomil. In the 2 week WD Phase, 77 subjects were exposed to azilsartan medoxomil and 103 subjects were exposed to placebo. In the 44 week OL Phase, 156 subjects were exposed to azilsartan medoxomil alone and 41 subjects were exposed to azilsartan medoxomil and other antihypertensives.

CHMP Rapporteurs comment

The efficacy data from the study AR14.001 was evaluated in detail during the Article 46 of Regulation (EC) No. 1901/2006 procedure for Edarbi (EMEA/H/C/002293/P46/012.1). The proposed text in section 5.1 describes the design of the study, the extent of the exposure to azilsartan medoxomil and the main efficacy results. In general, this is supported; however, modifications to the text are proposed to reflect the fact that dosing with azilsartan medoxomil started at 10 mg in DB and OL part of the study. Also, it is suggested to specify the numerical change from week 6/final visit of the DB phase to week 8/final visit of the WD phase in trough clinic seDBP between azilsartan medoxomil and placebo. Also, adaptations in the order of mentioning information in the text are proposed.

Overall, the following modifications are suggested:

Paediatric population

The antihypertensive effects of azilsartan medoxomil were evaluated in a Phase 3 randomized, double blind study in children or adolescents 6 to < 18 years of age with primary or secondary hypertension. This study involved a 6 week, double blind, randomized treatment phase (DB Phase), followed by a 2 week, double blind, randomized placebo controlled withdrawal phase (WD Phase). In the DB Phase, subjects were randomized (1:1:1:1) to the following groups: azilsartan medoxomil 10 mg, 20 mg, and 40 mg/80 mg (based on subject body weight), or losartan. **All patients started at the 10 mg treatment for 2 weeks; subsequently, patients either continued at 10 mg or were up-titrated to 20, 40, or 80 mg.** In the WD Phase, subjects were randomized (1:1) to continue taking their previously assigned active treatment or were switched to placebo. This study also included a 44 week, open label extension (OL Phase), in which all subjects received azilsartan medoxomil or azilsartan medoxomil and other antihypertensive medications as needed in a titrate to target blood pressure dosing algorithm, **starting at 10 mg azilsartan medoxomil**.

In the 6 week DB Phase, 162 subjects were exposed to azilsartan medoxomil. In the 2 week WD Phase, 77 subjects were exposed to azilsartan medoxomil and 103 subjects were

exposed to placebo. In the 44 week OL Phase, 156 subjects were exposed to azilsartan medoxomil alone and 41 subjects were exposed to azilsartan medoxomil and other antihypertensives.

In the 2 week withdrawal period, there was a loss of blood pressure control in subjects randomized to placebo, while subjects who remained on azilsartan medoxomil treatment had stable blood pressure control. **The difference in mean seated diastolic blood pressure change from Week 6 to Week 8 in the subjects treated with azilsartan medoxomil versus placebo was -5.42 mmHg (95% CI, -7.29 to -3.55 mmHg; p < 0.001).** ~~Subjects who were treated with azilsartan medoxomil (all doses pooled) had a statistically significantly greater change in mean seated DBP from baseline to Week 6 compared with losartan-treated subjects.~~ Percentage of subjects who achieved target blood pressure (defined as < 90th percentile for age, gender, and height) at Week 8 (week 2 of the withdrawal period) was significantly higher with azilsartan medoxomil treatment compared with placebo. **Subjects who were treated with azilsartan medoxomil (all doses pooled) had a statistically significantly greater change in mean seated DBP from baseline to Week 6 compared with losartan-treated subjects. The effect of azilsartan medoxomil remained consistent overtime during the open-label phase.**

~~In the 6 week DB Phase, 162 subjects were exposed to azilsartan medoxomil. In the 2 week WD Phase, 77 subjects were exposed to azilsartan medoxomil and 103 subjects were exposed to placebo. In the 44 week OL Phase, 156 subjects were exposed to azilsartan medoxomil alone and 41 subjects were exposed to azilsartan medoxomil and other antihypertensives.~~

Conclusion

In general, update of SmPC section 5.1 with the data from the paediatric study AR14.001 is supported. However, some modifications are proposed.

9.5 Update of SmPC section 5.2 with paediatric clinical data from Study TAK-491_109 (PIP study 7) following the outcome of procedure EMEA/H/C/002293/P46/011

The MAH proposes to update SmPC section 5.2 with paediatric clinical data from Study TAK-491_109. The following changes are proposed (Deleted text: ~~strike trough~~, additions: **bold underlined**):

Paediatric population
~~The pharmacokinetics of azilsartan have not been studied in children under 18 years of age.~~**. The pharmacokinetics of azilsartan following the oral doses of azilsartan medoxomil were evaluated in hypertensive children aged 6 to < 18 years in a single dose study as well as a multiple dose study of 10 mg to a maximum of 80 mg for 6 weeks. Based on population pharmacokinetic analysis, oral clearance (CL/F) and apparent volume of distribution (V/F) are correlated with body weight.**

CHMP Rapporteurs comment

Study TAK-491_109 was previously submitted and assessed in paediatric worksharing Article 46 procedure EMEA/H/C/002293/P46. During this initial assessment it was concluded that study TAK-491_109 was appropriate for first characterisation of the pharmacokinetics of azilsartan medoxomil in the pediatric population. However, the data were very limited for the youngest children (aged ≥1 to <6 years) and mainly based on modeling. The population PK model included oral clearance and apparent volume of distribution as a function of body weight. Based on this study, it was concluded that, for children weighing more than 50 kg, the adult dose could probably be used. For children weighing between 25 and 50 kg the dose should probably be half of the adult dose.

Also the population PK model of study AR14.001 has been previously assessed. It was concluded that the popPK model appears to describe the pharmacokinetics in the pediatric population reasonably well. Some overestimation was observed. According to the company; this may be possible be attributed to the actual incompliance; also the rough estimation of the nominal time after the last dose may have attributed to the overprediction observed.

So single dose and steady state data are now available for children aged 6 years and older were and population models were consistent between studies. It was shown that the PK of azilartan medoxamil is linear and similar to the PK in adults when allometric scaling is applied. Dosing in children should be performed based on body weight.

The proposed update SmPC section 5.2 is not informative. Oral clearance (CL/F) and apparent volume of distribution (V/F) are always correlated with body weight. Such general statement is not acceptable.

It is agreed that there are insufficient data for children aged ≥1 to <6 years to support an update of the SmPC section 5.2.

The Applicant is asked to mention that exposure of azilsartan is dependent on body weight and a comparison to adult data should be made. Preferably, simulated exposure data for typical patients with bodyweight of 25 kg and 50 kg should be presented at the studied doses.

Conclusion

SmPC section 5.2 with PK data on children aged 6 to < 18 years should be updated with more informative data on the pharmacokinetics in children. The Applicant is asked to mention that exposure of azilsartan is dependent on body weight when allometric scaling is applied and a comparison to adult data should be made. Preferably, simulated exposure data for typical patients with bodyweight of 25 kg and 50 kg should be presented at the studied doses.

9.6 Update of SmPC section 5.3 with data from juvenile animal toxicity studies.

The Applicant added the following new information on juvenile oral toxicity studies in rats in SmPC section 5.3:

Juvenile animal studies

A number of pilot and definitive juvenile oral toxicity studies ranging from 7 days to 3 months in duration examined the effects of azilsartan medoxomil, alone or in combination with M-II, on rat pups initiated at different ages ranging from post-natal day [PND] 0 [newborn] to PND 21. The results of these studies suggest that juvenile rats are more susceptible to angiotensin-related altered renal morphology and function throughout the first 2 postnatal weeks, corresponding with the period of nephrogenesis. Species differences in renal development between rats and humans should be considered when interpreting the effects of ARBs in juvenile rats relative to human safety. The incomplete development of the renal system in human infants formed the basis for a waiver for investigation of azilsartan medoxomil in paediatric subjects < 2 years of age.

CHMP Rapporteurs comment

The text is not in good order and should be amended. The text is unnecessarily long and PND 0 should be PND 14. Also, the major findings of only pivotal studies should be mentioned. The following text is recommended:

Juvenile animal studies

Juvenile oral toxicity studies up to 3 months in duration in rats (2 or 3 weeks old) with azilsartan medoxomil, alone or in combination with M-II, showed that juvenile rats may be more susceptible to angiotensin-related altered renal morphology and function when

exposed from postnatal week 2, corresponding with the period of growth and maturation of the renal system. The growth and maturation stage of the human renal system extends to about 2 years of age."

10. Request for supplementary information

10.1. Major objections

None

10.2. Other concerns

Non clinical aspects

1. In general, an update of SmPC section 5.3 with the data from juvenile oral toxicity studies in rats is supported. However, some modifications to the text are proposed in section 9.

Clinical aspects

2. In general, an update of SmPC section 5.1 with the data from the paediatric study AR14.001 is supported. However, some modifications are proposed in section 9.
3. SmPC Section 5.2 with PK data on children aged 6 to < 18 years should be updated with more informative data on the pharmacokinetics in children. The Applicant is asked to mention that exposure of azilsartan is dependent on body weight when allometric scaling is applied, and a comparison to adult data should be made. Preferably, simulated exposure data for typical patients with bodyweight of 25 kg and 50kg should be presented at the studied doses.

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

11.1. Major objections

None

11.2. Other concerns

Non clinical aspects

Question 1

In general, an update of SmPC section 5.3 with the data from juvenile oral toxicity studies in rats is supported. However, some modifications to the text are proposed in section 9.

Summary of the MAH's response

Assessment of the MAH's response

The MAH has agreed with the proposed changes.

Conclusion

Issue resolved.

Clinical aspects

Question 2

In general, an update of SmPC section 5.1 with the data from the paediatric study AR14.001 is supported. However, some modifications are proposed in section 9.

Summary of the MAH's response

The MAH agrees with the agency proposal, and section 5.1 of the SmPC has been updated accordingly.

Assessment of the MAH's response

The MAH has agreed with the proposed changes.

Conclusion

Issue resolved.

Question 3

SmPC Section 5.2 with PK data on children aged 6 to < 18 years should be updated with more informative data on the pharmacokinetics in children. The Applicant is asked to mention that exposure of azilsartan is dependent on body weight when allometric scaling is applied, and a comparison to adult data should be made. Preferably, simulated exposure data for typical patients with bodyweight of 25 kg and 50kg should be presented at the studied doses.

Summary of the MAH's response

The MAH confirms that the SmPC section 5.2 has been updated accordingly to include the required information as proposed by the agency.

Section 5.2 of the SmPC has been modified as follows:

"The population pharmacokinetics of azilsartan following oral doses of azilsartan medoxomil were evaluated in hypertensive children aged 6 to < 18 years in a single dose study as well as in a multiple dose study of 10 mg to a maximum of 80 mg for 6 weeks. Geometric means of estimates for the maximum concentration at steady-state (Cmax,ss) and steady-state area under the time-concentration curve (AUCss) of azilsartan generally increased in proportion to dose within each of 3 body weight groups (≥25, ≤50 kg; >50, ≤75 kg; and >75, ≤150 kg). Dose-normalized exposure parameter estimates for TAK-536 AUCss, Cmax,ss, and average concentration at steadystate (Cavg,ss) using the model were generally higher for pediatric patients weighing ≤50 kg compared to those weighing >50 kg. Exposure of azilsartan was dependent on body weight and similar to the PK in adults when allometric scaling was applied."

Assessment of the MAH's response

SmPC section 5.2 has been revised. As requested the updated text mentions that the exposure of azilsartan is dependent on body weight when allometric scaling is applied. The MAH did not provide simulations for typical patients with bodyweight of 25 kg and 50kg, but provides very detailed information on the design of the modelling experiments. The text can be shortened to improve readability:

"The population pharmacokinetics of azilsartan following oral doses of azilsartan medoxomil were evaluated in hypertensive children aged 6 to < 18 years in a single dose study as well as in a multiple dose study of 10 mg to a maximum of 80 mg for 6 weeks. ~~Geometric means of estimates for~~ **Generally, a dose proportional increase of** the maximum concentration ~~at steady-state~~ (Cmax,ss) and ~~steady-state area under the time-concentration curve~~ **exposure** (AUCss) of azilsartan ~~generally increased in proportion to dose within each of 3 body weight groups (≥25, ≤50 kg; >50, ≤75 kg; and >75, ≤150 kg)~~ **was observed**. ~~Dose-normalized~~ **E**xposure **of azilsartan was dependent on body weight,** ~~parameter estimates for TAK-536 AUCss, Cmax,ss, and average concentration at steadystate (Cavg,ss) using the model were~~ generally **a** higher **exposure** for pediatric patients weighing ⩽50 kg compared to those weighing >50 kg. **The azilsartan** exposure ~~of azilsartan~~ was ~~dependent on body weight and~~ similar ~~to the PK in~~ **between children and** adults when allometric scaling was applied."

Summarized: "The population pharmacokinetics of azilsartan following oral doses of azilsartan medoxomil were evaluated in hypertensive children aged 6 to < 18 years in a single dose study as well as in a multiple dose study of 10 mg to a maximum of 80 mg for 6 weeks. Generally, a dose proportional increase of the maximum concentration (Cmax,ss) and exposure (AUCss) of azilsartan was observed. Exposure of azilsartan was dependent on body weight, generally a higher exposure was observed for pediatric patients weighing ⩽50 kg compared to those weighing >50 kg. The azilsartan exposure was similar between children and adults when allometric scaling was applied."

Conclusion

Issue is partially resolved. Some additional changes of the wording are requested, as indicated above.

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

12.1. Major objections

None

12.2. Other concerns

Clinical aspects

Question 1

SmPC section 5.2: Some additional changes of the wording are requested.

Summary of the MAH's response

The MAH agrees with the agency proposal, and section 5.2 of the SmPC has been updated accordingly.

Assessment of the MAH's response

The MAH has agreed with the proposed changes.

Conclusion

Issue resolved.

Conclusion

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