EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2013
EMA/696794/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procoralan

International non-proprietary name: ivabradine

Procedure No. EMEA/H/C/000597/II/0029

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Les Laboratoires Servier submitted to the European Medicines Agency on 13 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Procoralan	ivabradine	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	II

The MAH proposed the update of sections 4.3 and 4.6 of the SmPC in order to extend the current contra-indication during pregnancy and breastfeeding to women of child-bearing potential not using appropriate contraceptive measures. In addition, the description of the luminous phenomena (phosphenes) and vision blurred were added to section 4.8 of the SmPC according to information from post-marketing experience and “diplopia” and “visual impairment” were included as undesirable effects in section 4.8 of the SmPC. The changes described above were requested following recommendations from the PRAC Assessment Report for PSUR No 8. The Package Leaflet was proposed to be updated accordingly.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.3.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	13 August 2013
Start of procedure:	22 September 2013
Rapporteur’s preliminary assessment report circulated on:	24 October 2013
Rapporteur’s updated assessment report circulated on:	15 November 2013
CHMP opinion:	21 November 2013

2. Scientific discussion

2.1. Introduction

Procoralan / Corlentor, containing ivabradine hydrochloride, is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine is approved for:

- *Treatment of coronary artery disease*
- *Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm.*

  Ivabradine is indicated:

  - *in adults unable to tolerate or with a contra-indication to the use of beta-blockers*
  - *or in combination with beta-blockers in patients inadequately controlled with an optimal beta- blocker dose and whose heart rate is > 60 bpm.*
- *Treatment of chronic heart failure: Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.*

The product is registered through the Centralised Procedure since 25 October 2005.

Based on the assessment report of the PSUR No 8 for Corlentor/Procoralan with a DLP 25 October 2012, the PRAC recommended that the MAH should submit the following variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so within 2 months:

- regarding the use of ivabradine during pregnancy and lactation based on the corresponding cases both from post-marketing sources and from the SHIFT-trial;
- update of section 4.8 of the SmPC regarding visual impairment and diplopia. Visual impairment and diplopia might be linked with the listed events of phosphenes/photopsia and vision blurred in some cases. However, in the majority of the cases the events were reported separately and without reference to the listed terms. Due to high number of reported cases, and presence of dechallange and rechallanges cases, it is more appropriate to include visual impairment and diplopia in section 4.8 as separate ADRs. The MAH should include proposed frequencies for these ADRs in accordance with the SmPC guideline.

Current variation was submitted to extend the contra-indication during pregnancy and breastfeeding (present already in the SmPC since the Marketing Authorisation) to women of child-bearing potential not using appropriate contraceptive measures as ivabradine was associated with cardiac teratogenicity in rats and ectrodactylia in rabbits, and to improve prescribers' awareness, by extending the description of the luminous phenomena (phosphenes) and vision blurred in the SmPC according to information from post-marketing experience and adding "diplopia" and "visual impairment" as undesirable effects in section 4.8 further to PRAC recommendation.

2.2. Clinical Safety aspects

2.2.1 Women of childbearing potential not using appropriate contraceptive measure

In the PSUR n°8 for ivabradine, covering the period 25.10.2009 to 25.10.2012, it was recommended to reflect on the need of the Product Information update with regards to a statement regarding women of childbearing potential, to extend the contraindications during pregnancy and breastfeeding (present in the SmPC since the Marketing Authorisation) to women of childbearing potential not using appropriate contraceptive measure, as ivabradine was associated with cardiac teratogenicity in rats and ectrodactylia in rabbits.

Since the initial registration, the SmPC of ivabradine states that the use of ivabradine is contraindicated during pregnancy and breastfeeding as pre-clinical investigations revealed that, pregnant animals, treated with ivabradine during organogenesis at exposures close to therapeutic doses, showed a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit. During the period covered by PSUR n°8, cases of pregnancy (including cases from the SHIFT study) in patients treated with ivabradine were reviewed. The therapeutic indications of ivabradine are unlikely to concern women of child-bearing potential; however, to reinforce the contraindications during pregnancy and breastfeeding present in the SmPC since the Marketing Authorisation, it was proposed to discuss the need for the update of a statement regarding women of childbearing potential.

Clinical trial cases

Overall, 5 cases of study drug exposure during pregnancy were reported in clinical trials. Two cases were reported in healthy volunteers included in phase 1 studies (1 day exposure) while the remaining 3 cases occurred in the SHIFT study (CL3-16257-063) conducted in patients with chronic heart failure. Following unblinding, this cases distributed in 1 case exposed to ivabradine and 2 exposed to placebo.

Cumulative data of exposure to ivabradine or placebo and outcomes are presented in the following tables.

Table 1 - Cumulative data of exposure to ivabradine during pregnancy over cumulative period from clinical trials

Pregnancy outcome	N	Period of Exposure	Clinical Trial
Spontaneous abortion	0		
Induced abortion	1	1st trimester, W1 to W4	CL3-16257-063 Cardiac failure chronic
Foetal death (Congenital anomaly)	0		
Live birth	0		
- Normal baby	2	1st trimester in 2 cases: - 20 mg, 1 day in 2 phase 1 CT	CL1- 16257- 049 CL1- 16257- 029
- Normal delivery (Congenital anomaly)	0		-
- Premature (Congenital anomaly)	0		
Lost to follow-up	0	-	
Follow-up in progress	0	-	

Table 2 - Cumulative data of exposure to placebo during pregnancy over cumulative period from clinical Trials

Pregnancy outcome	N	Period of Exposure	Clinical Trial
Spontaneous abortion	0		
Induced abortion	1	1st trimester, D1 to D30	CL3-16257-063 Cardiac failure chronic
Foetal death (Congenital anomaly)	0		
Live birth	0		
- Normal baby	1	1st trimester D1 to D35	CL3-16257-063 Cardiac failure chronic
- Normal delivery (Congenital anomaly)	0		-
- Premature (Congenital anomaly)	0		
Lost to follow-up	0	-	
Follow-up in progress	0	-	

Post-marketing experience

Since marketing authorisation until 25 April 2013 (data lock point (DLP) of PSUR n°9, submitted on July 3rd 2013), a total of 15 cases of patients exposed to ivabradine during pregnancy were reported from post-marketing experience. These patients were treated with ivabradine for tachycardia (9/15) or ischaemic cardiopathy (2/15), vasovagal syncope (1/15), the indication being unknown in the remaining cases (3/15). Cumulative data of pregnancies and outcomes are presented in the following table.

Table 3 - Cumulative data of exposure to ivabradine during pregnancy from post-marketing experience

Pregnancy outcome	N	Period of Exposure
Spontaneous abortion	0	
Induced abortion	2	1st trimester (D0 to W4) in both cases
Foetal death (Congenital anomaly)	0	
Live birth	8	
- Normal baby	8 (1 foetal growth retardation**)	1st trimester in 7 cases: - D0 to W3 in 1 case - D0 to W4 in 2 cases - D0 to W9 in 1 case* - D0 to W10 in 1 case - D0 to W12 in 1 case - D0 to Unknown in 1 case** 1st and 3rd trimester in 1 case - D0 to unknown then W34 to W37.
- Normal delivery (Congenital anomaly)	0	
- Premature (Congenital anomaly)	0	
Lost to follow-up	4 (1 normal echo at W21)	1st trimester in 3 cases: - D0 to W3 in 1 case - D0 to W10 in 1 case - D0 to W10 in 1 case 1st and 2nd trimester in 1 case: - D0 to W17 in 1 case
Follow-up in progress	1	1st and 2nd trimester in 1 case: - D0 to M6 in 1 case

** According to follow-up information received post-DLP: caesarean section was indicated at the 36th week post-LMP (34th week of pregnancy) due to foetal growth stop. Birth weight 2120 g; No malformation; Apgar 9-10; No medical problem at the maternity reported*

*** Delivery was induced due to harmonious in utero Foetal growth retardation (37.7 weeks of amenorrhea, 2510g, height 46cm and cranial perimeter 30.5cm).Investigations were negative for CMV. Mother with aortic valvular insufficiency, Marfan's syndrome since 30-APR-1978, pulmonary embolism in 1988, recurrent pneumothorax in 2005 (resulting in lung lobectomia) and smoking along her pregnancy (quantity not specified). Metoprololol was continued during the whole duration of the pregnancy. Other treatments taken during the pregnancy included: Aspirin cardio, enoxaparin sodium, pantoprazole.*

Following this cumulative review of pregnancy cases in patients treated with ivabradine, including cases from the SHIFT study, the MAH proposed, in order to reinforce this restriction, to add, in section 4.3 of the SmPC, a contraindication to the use of ivabradine in ***"women of child-bearing potential not using appropriate contraceptive measures"***.

The MAH also proposes to add, in section 4.6 of the SmPC, the corresponding following statement:

"Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during

treatment (see section 4.3)."

The CHMP noted that the MAH provided a cumulative review of pregnancy cases in patients treated with ivabradine, including cases from the SHIFT study. Based on this review the MAH proposes to include women of child-bearing potential not using appropriate contraceptive measures in the contra-indication "pregnancy and lactation". The CHMP agreed with this proposal.

In addition the MAH has formulated a contraindication for breast-feeding. This was also considered acceptable. However, the CHMP proposed to add:

"Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child."

2.2.2 Visual impairment and diplopia

The MAH agreed to include visual impairment and diplopia in section 4.8 as separate ADRs and to calculate frequencies as advised.

Based on the "Guideline on Summary of Product Characteristics", rev. 2 dated September 2009, the MAH estimated adverse reactions frequencies of "Diplopia" and "visual impairment", corresponding to the MedDRA Preferred Term (PT) "Diplopia" and "Visual impairment" or "Visual disturbance" respectively (the PT "Visual impairment" did not exist in the MedDRA dictionary version in force of that of study 057 and 063), in patients treated with ivabradine was estimated in 3 different sets :

- the Integrated Analysis of Safety (IAS): data used to calculate frequency of adverse events for the initial version of ivabradine SmPC (data pooled on 5 mg and 7.5 mg doses);
- the study CL3-057 (study which supported the extension of indication of ivabradine in combination with beta-blockers in angina patients).
- the study CL3-063 (study which supported the extension of indication of ivabradine in Chronic Heart Failure).

For these last two studies, it has to be noted that the PT "visual impairment" did not exist in the MedDRA dictionary version in force at time of study 057 and 063: the PT "visual disturbance" was used instead.

Moreover, in line with the guideline, in case of different frequencies observed between sets, "the highest frequency" was chosen.

The frequencies of the emergent adverse events (EAEs) “Diplopia” and “Visual impairment” observed in the 3 sets of patients are summarised in the table below:

EAE (PT)	IAS N°1 Ivabradine (5+7,5mg bid) N= 1605 n(%)	CL3-057 Ivabradine (5 or 7.5 mg bid) N = 449 n(%)	CL3-063 Ivabradine (2.5, 5 or 7.5 bid) N = 3232 n(%)	Corresponding MedDRA frequency
Diplopia	11 (0.7%)	1 (0.2%)	1 (0.03%)	**uncommon**
Visual impairment	*	-	-	-
Visual disturbance	*	1 (0.2%)	3 (0.09%)	**uncommon**

IAS: Integrated Analysis of Safety; N: Number of patients receiving ivabradine

*As stated in the response document to PRAC Rapporteur PAR (Appendix 1), in the angina clinical development program, the main analysis of visual symptoms was carried out in the visual disturbances subset (VDS), consisting of patients in the 5 studies (017, 018, 019, 021, 023, and 030, which together involved 2 545 patients treated with ivabradine. In these studies, visual symptoms were collected using standardised charts and were reviewed by an Ophthalmic Safety Subcommittee. The committee coded the visual symptoms reported by patients into standard ophthalmic terms, which were then grouped into three classes, 'phosphene-like', 'vision blurred', and 'other visual symptoms' and were specifically recorded and assessed. In this classification, there was no term equivalent to visual disturbance or visual impairment. Hence, no visual symptoms remained with the non specific code of visual disturbance /visual impairement.

Additionally, in the post-marketing experience, the majority of the suspected adverse reactions involving visual manifestations were luminous phenomena and vision blurred. These reports, while presenting similar features as those reported during clinical trials, provide detailed descriptions of the various presentation of the luminous phenomena or vision blurred experienced by the patients, beyond the current description given in the SmPC: spot lines, bright lines, coloured effects, shadowing effect (halo, multiples images, ghost images) or stroboscopic or kaleidoscopic effect (image decomposition) also reported sometimes as feeling of increased sensibility to the light.

Therefore, in order to improve prescriber’s awareness, the MAH proposed to extend the description of the luminous phenomena (phosphenes) in the section 4.8 of SmPC to reflect visual symptoms description arising from post-marketing experience as follows:

> ‘Description of selected adverse reactions
>
> Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. **Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image (retinal persistency).** The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes’.

The PIL was proposed to be updated accordingly to improve patient’s awareness. Moreover, the MAH also took the opportunity to add in the PIL a patient’s friendly term for vision blurred: i.e. ‘cloudy vision’.

The CHMP commented that the MAH included visual impairment and diplopia in section 4.8 as separate ADRs and calculated frequencies. However, the MAH did not assign a frequency category to the ADR ‘visual impairment’. For adverse reactions that have never been observed in clinical trials, the SmPC Guideline states that then the upper limit of the 95% confidence interval is not higher than 3/X, with X representing the total sample size summed up across all relevant clinical trials and studies (e.g. those with a follow-up long enough to detect the adverse reaction). In this case, visual impairment has not been observed among 1,605+449+3,232 (=5,826) subjects exposed to the product in clinical trials and studies, then the upper limit of the 95% confidence interval for the point estimate is 1/1,762 or less and the frequency category should be "rare", based on worst value of the point estimate. Therefore, the MAH

was requested to assign the frequency 'rare' to the ADR 'visual impairment'. The additional sentence to further describe the manifestation of phosphenes was accepted by the CHMP.

In response, the MAH explained that the frequency of both undesirable effects "diplopia" and "visual impairment" was estimated, according to the "Guideline on Summary of Product Characteristics (SmPC)", rev. 2 dated September 2009, based on data from "each adequately designed study where this adverse reaction could have been detected". Based on these data, the frequency "uncommon" has been assigned to the 2 undesirable effects proposed to be added, i.e. "diplopia" and "visual impairment".

The MAH emphasized as well that, regarding "visual impairment", the specific Preferred Term (PT) "visual impairment" did not exist in the MedDRA dictionary version in force at time of clinical studies ASSOCIATE (057) and SHIFT (063) (clinical studies that have led to the extensions of indication of ivabradine). Therefore another Preferred Term, namely "visual disturbance" was used to assign frequency of "visual impairment". Based on the above elements, it is proposed to maintain the frequency "uncommon" for the 2 undesirable effects proposed to be added, i.e. "diplopia" and "visual impairment". The argumentation of the MAH was supported by the CHMP.

2.3. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI) (displayed **in bold underlined**):

4.3 Contraindications

- Pregnancy, lactation **and women of child-bearing potential not using appropriate contraceptive measures** (see section 4.6)

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy

There are no or limited amount of data from the use of ivabradine in pregnant women.

Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy (see section 4.3).

Breastfeeding

Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding (see section 4.3).

Fertility

Studies in rats have shown no effect on fertility in males and females (see section 5.3).

The CHMP agreed that the contraindication in pregnancy is extended to women of child-bearing potential not using appropriate contraceptive measures. This was agreed by the CHMP. In addition the MAH has

formulated a contraindication for breast-feeding. This was also considered acceptable by the CHMP. However, the CHMP proposed to modify the sentence in the following way:

"Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child."

This was accepted by the MAH.

4.8 Undesirable effects

Summary of the safety profile

Ivabradine has been studied in clinical trials involving nearly 14,000 participants.

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

Tabulated list of adverse reactions

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
	Uncommon*	**Diplopia**
		Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	Atrial fibrillation
		AV 2nd degree block, AV 3rd degree block
		Sick sinus syndrome
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation
		Diarrhoea

Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood
		ECG prolonged QT interval

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Description of selected adverse reactions

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. **Phosphenes may also be described as a halo, image decomposition (stroboscopic or kaleidoscopic effects), coloured bright lights, or multiple image (retinal persistency).** The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

Consequential changes to the PIL were considered acceptable by the CHMP.

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

The CHMP believes that the amendments to sections 4.3, 4.6 and 4.8 of the SmPC do not change the benefit/risk balance of ivabradine that remains positive.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	II

Update of sections 4.3 and 4.6 of the SmPC in order to extend the current contra-indication during pregnancy and breastfeeding to women of child-bearing potential not using appropriate contraceptive measures. In addition, the description of the luminous phenomena (phosphenes) and vision blurred were added to section 4.8 of the SmPC according to information from post-marketing experience and “diplopia” and “visual impairment” were included as undesirable effects in section 4.8 of the SmPC. The changes described above were requested following recommendations from the PRAC Assessment Report for PSUR No 8. The Package leaflet was updated accordingly. Furthermore, the PI was brought in line with the latest QRD template version 9.3.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.