EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/CHMP/220046/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Invented name Aprovel

Procedure No. EMEA/H/C/000141/II/0148

Marketing authorisation holder (MAH): Sanofi Pharma Bristol-Myers Squibb SNC

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 7523 7455
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, Sanofi Pharma Bristol-Myers Squibb SNC submitted to the European Medicines Agency on 7 February 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Aprovel	irbesartan	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.3.b	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II

The MAH proposed an update of SmPC sections 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to align the annexes with the latest QRD template, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet.

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

Rapporteur: Concepcion Prieto Yerro

1.2. Steps taken for the assessment

Submission date:	7 February 2013
Start of procedure:	24 February 2013
Rapporteur's preliminary assessment report circulated on:	27 March 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2013
MAH's responses submitted to the CHMP on:	5 June 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 June 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	20 June 2013
CHMP opinion:	27 June 2013

2. Scientific discussion

2.1. Introduction

Irbesartan is a non-peptide angiotensine II-receptor antagonist (angiotensin receptor blocker (ARB)) with high selectivity for the At1 subtype. Bristol-Myers Squibb (BMS) and Sanofi-Synthélabo Pharma have jointly developed this compound and the International Birth Date is 12 August 1997. Irbesartan is available as monotherapy or as a fixed dose combination with hydrochlorothiazide (HCTZ), a thiazide diuretic.

The MAH has three different duplicate medicinal products containing irbesartan currently approved in the EU through the centralised procedure: Aprovel, Karvea and Irbesartan Zentiva. Irbesartan is indicated for the treatment of hypertension and for the treatment of renal disease in hypertensive type 2 diabetic patients, being available in 75, 150 or 300 mg tablets for oral administration.

In addition, the MAH has three different duplicate fixed combination medicinal products currently approved in the EU through the centralised procedure: CoAprovel, Karvezide and Irbesartan Hydrochlorothiazide Zentiva. The fixed dose combination is indicated for treatment of essential hypertension in adult patients whose blood pressure is not adequately controlled on irbesartan or HCTZ alone.

On 19 December 2011, the MAH for aliskiren (Novartis), informed the EMA of its intention to terminate the ALTITUDE study in patients with type 2 diabetes at high risk for cardiovascular and renal events following a recommendation by the independent Data Monitoring Committee (DMC). Aliskiren is a selective direct inhibitor of human renin that inhibits the renin-angiotensin system (RAAS) blocking the conversation of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin II. Aliskiren is approved for the treatment of hypertension, and is provided in medicinal products containing aliskiren only as well as in fixed-dose combination medicinal products (in combination with amlodipine, with hydrochlorothiazide, and with both amlodipine and hydrochlorothiazide).

The ALTITUDE study was designed to test the hypothesis that the addition of aliskiren to the treatment of type 2 diabetic patients with nephropathy would result in improved cardiovascular and renal outcomes. On 14 December 2011, the DMC recommended the study termination concluding that in the study arm of patients receiving aliskiren when added on to conventional treatments for hypertension (either angiotensin-converting enzyme inhibitors (ACEi) or ARB), patients were unlikely to benefit from treatment. In addition, an increased incidence of non-fatal stroke, renal complications, hyperkalaemia and hypotension was observed. Therefore, on 20 December 2011, the CHMP assessed all the available data and its impact on the benefit-risk balance for aliskiren- containing medicinal products as part of a referral procedure. The conclusion of the CHMP review of all interim data available from the ALTITUDE study and all data from other studies and post-marketing spontaneous reports suggested an increased risk of adverse cardiovascular outcomes (hypotension, stroke, hyperkalaemia) and changes in renal function when aliskiren is combined with ARBs or ACEi, especially in diabetic patients and those with impaired renal function. The CHMP recommended the contraindication of the use of aliskiren containing medicines in combination with ARBs or ACEi in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 ml/min). In addition, the CHMP concluded for all other patient groups that the use of aliskiren in combination with ARBs or ACEi is not recommended for the overall patient population.

In view of the CHMP recommendation for inclusion of a contraindication of the concomitant use of aliskiren-containing medicines with ACEi and ARBs, the MAH has now submitted a type II variation accordingly to reflect this change in the product information of their irbesartan- and irbesartan hydrochlorothiazide-containing medicinal products (see above).

The amended sections of the Summary of Product Characteristics (SmPC) are 4.3 "Contraindications", 4.4 "Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction", as well as section 2 " What you need to know before you take "TRADENAME" of the Package Leaflet. In addition, the MAH took the opportunity of this Type II variation to align the product information with QRD template 8 version 2, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet.

As part of the variation application, the MAH has provided a comprehensive medical safety assessment of the risk of the combination of irbesartan (or irbesartan + HCTZ) with aliskiren in patients with diabetes or with renal impairment, in support of the proposed changes to the product information. The events of particular interest in this assessment are: hyperkalaemia, hypotension, renal failure, and stroke.

2.2. Clinical Safety aspects

2.2.1. Methods – analysis of data submitted

Estimated drug exposure

An estimate of the number of treated patients is derived from sales figures received from IMS Health. Due to limitations with historical sales data, IMS was only able to retrieve sales data from 01 July 1997 to 30 September 2012. No data is yet available for the fourth quarter of 2012. These figures, which represent the bulk of BMS worldwide sales, remain an approximation of the total quantity sold.

Corporate safety database (CARES) search results

A comprehensive, cumulative search of the CARES was performed using MedDRA v14.1 to identify all spontaneous, literature cases, and clinical trial cases in which irbesartan or irbesartan + HCTZ was taken in combination with aliskiren containing medicines. All reports were received by BMS during the post-marketing experience with irbesartan or irbesartan + HCTZ from the period covering 12 August 1997 through 26 November 2012.

Irbesartan and aliskiren

During the reporting period, a total of 15 healthcare professional confirmed (HCP) initial adverse event cases were received that included irbesartan and aliskiren containing medicines as a suspect, concomitant, or interacting drug. Of the 15 HPC cases, 8 were spontaneously reported and 7 were received from Phase I-IV clinical trials. Of the 15 total cases, 9 were serious (2 spontaneous cases and 7 clinical trial cases). There were 3 events with a fatal outcome (with 2 of the events involving the same patient) among the total 15 HCP cases; in the first case the patient died due to incidental aspiration and acute respiratory failure which were unrelated to irbesartan or aliskiren therapy, and in the second case the patient died due to cerebral hemorrhage that was assessed as not related to irbesartan therapy. Additionally, 6 spontaneous, non-HPC cases were received. No non-HPC fatal outcomes were reported.

Among the 21 cases identified, there were 14 males and 7 females who ranged in age from 47 to 89 years (Mean = 68.3 years). Overall, the causality assessment by reporter of the 11 reports included 5 not related, 2 probably related, 1, possibly related, and 1 not likely related. In 12 reports causality was not provided. Of the 21 cases, 7 cases had a positive dechallenge, in 6 cases irbesartan therapy was

ongoing, in 6 cases dechallenge/rechallenge was not provided, and 2 cases had a negative dechallenge. Furthermore, in one case the event reappeared when the patient was switched to valsartan therapy, in one case the event reappeared when the patient was switched to atenolol, and in another case the patient experienced an unexpected benefit of improved mood. Overall, 3 of the 21 cases included: hyperkalaemia (1), hypotension (1), renal failure (0), or stroke (1).

Irbesartan +HCTZ and aliskiren

During the reporting period, a total of 5 HCP initial adverse event cases were received. Of the 5 HPC cases, 3 were spontaneously reported from worldwide sources and 2 were received from Phase IV clinical trials. Of the 5 total cases, all 5 qualified for classification as serious: 3 spontaneous cases and 2 Phase IV clinical trial cases. No fatal outcomes were reported. Additionally, 4 non-HPC cases were received: 3 spontaneous cases and 1 Phase IV clinical trial case. Of the 4 total cases, 1 qualified for classification as serious. No fatal outcomes were reported. Among the 9 cases identified, there were 4 males and 5 females who ranged in age from 35 to 90 years (Mean = 63 years, N = 8). Overall, the causality assessment by reporter of the 9 reports included 1 certainly related, 1 probably related, and 1 possibly related. In 6 reports a reporter causality assessment was not provided. Of the 9 cases, in 5 cases irbesartan therapy was ongoing, 3 cases had a positive dechallenge, and in 1 case dechallenge/rechallenge information was not provided. Furthermore, in one case the patient experienced a positive dechallenge when aliskiren was stopped and irbesartan was continued. Overall, 4 of the 9 cases included: hyperkalaemia (2), hypotension (1), renal failure (1), or stroke (1) (Note: Renal failure and Stroke occurred in the same patient.)

Literature review

Additionally, a search of the published scientific literature was performed to identify any articles related to the use of irbesartan or irbesartan + HCTZ in combination with aliskiren. For each set of references retrieved, titles were screened for possible relevance to the subject. The following databases were searched: MEDLINE, EMBASE Alert, EMBASE, Derwent Drug File, Biosis Previews, and Int. Pharm Abs. Following review of the relevant articles, the MAH concluded that the search did not reveal any additional information that was not already reported in the CHMP assessment report for the referral procedure.

The articles summarized below met the search criteria for possible drug interactions involving irbesartan and aliskiren + HCTZ; irbesartan and aliskiren + valsartan; irbesartan and aliskiren fumarate/Tekturna/Rasilez; irbesartan + HCTZ and aliskiren + HCTZ; irbesartan and aliskiren + valsartan; or irbesartan and aliskiren fumarate/Tekturna/Rasilez.

- Parving H, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med, 2012;367:2204-13. This article refers to the results of the ALTITUDE study.
- Parving H, Brenner BM, McMurray JJ, et al. Aliskiren trial in type 2 diabetes using cardiorenal endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 2009;24:1663-71.
- Lillyblad MP, Knutson AR, Philbrick AM, et al. Aliskiren alone or in combination for the treatment of mild-to-moderate hypertension: current role and future perspectives. J Pharm Technol 2012;28:16-25.
- O'Brien E, Barton J, Nussberger J, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin converting enzyme inhibitors, or an angiotensin receptor blocker. Hypertension 2007;49:276-84.
- Vaidyanathan S, Jarugala V, Dieterich HA, et al. Clinical pharmacokinetics and pharmacodynamics of aliskiren. Clin Pharmacokinet. 2008;47(8):515-31.

- Volpe M, Danser AJH, Menard J, et al. Inhibition of the renin-angiotensin-aldosterone system: is there room for dual blockage in the cardiorenal continuum? J Hypertension 2012;30:647-54.

MAH's conclusions

Overall, the results of the underlying medical safety assessment including the cumulative review of irbesartan global safety surveillance data and the comprehensive literature review were consistent with the information included in the CHMP assessment report for the aliskiren referral procedure.

2.2.2. Discussion

In February 2012, the CHMP completed a review of aliskiren-containing medicines (primarily based on data from the ALTITUDE trial), recommending that these medicines should be contraindicated in patients with diabetes or moderate to severe renal impairment who take ACEis or ARBs. In addition, a warning was included to highlight that the combination of aliskiren with an ACEi or ARB is not recommended in all other patients (EMA/CHMP/112042/2012).

Since the outcome of the referral procedure, a number of publications have been made publicly available concerning the efficacy and safety of dual blockade of the renin-angiotensin-aldosterone system (RAAS). Specifically, a recently published meta-analysis by Makani[1] on the dual RAAS blockade with ARBs, ACEi or direct renin inhibitors (aliskiren) raised safety concerns for this therapeutic approach. Briefly, the authors of that meta-analysis showed that dual blockade of the RAAS (compared with monotherapy) was not associated with a clinical benefit in reducing all-cause mortality (relative risk [RR] = 0.97; 95%CI 0.89-1.06) and cardiovascular mortality (RR= 0.96; 0.88-1.05), but was associated with a reduction in admissions to hospital for heart failure (RR=0.82, 0.74-0.92). In addition, dual blockade was associated with an increased risk of hyperkalaemia (RR=1.55; 1.32-1.82), hypotension (RR=1.66; 1.38-1.98) and renal failure (RR=1.41; 1.09-1.84). According to the authors, efficacy and safety results were consistent in cohorts with and without heart failure when dual blockade was compared with monotherapy except for all-cause mortality, which was higher in the cohort without heart failure, and renal failure which was shown to be significantly higher in the cohort with heart failure.

The CHMP is aware that additional relevant results (not included in the search provided by the MAH) have been published recently. A brief meta-analysis in the diabetic population[2], with a high degree of overlap with the included trials by Makani et al., showed that diabetic patients receiving dual blockade tended to have a higher risk (vs. monotherapy) of hyperkalemia, hypotension and kidney damage, with no reduction in overall mortality. An alternative recent meta-analysis of trials in chronic kidney disease, showed that dual RAAS blockade was associated with an increased risk of hyperkalemia and hypotension, but there was no effect on doubling of the serum creatinine, hospitalization or mortality relative to monotherapy[3].

Along the same line, in a recent re-analysis of the "ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial ACE-inhibitors (ONTARGET)" trial[4] in people with diabetes and renal disease, cardiovascular and kidney outcomes (dialysis or doubling of serum creatinin) did not differ between dual blockade with ARB/ACEi (telmisartan/ramipril) and monotherapy, but acute dialysis (HR=1.55; 0.84-2.85), hyperkalemia (HR=1.71; 1.44-2.02) and hypotension (HR=2.30; 1.74-3.04) tended to be more frequent with dual therapy.

More recently, the U.S. Veterans Affairs Cooperative Study "Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D)" was terminated early due to a greater number of observed acute kidney injury events and hyperkalemia in the dual blockade therapy group (ARB/ACEi: losartan/lisinopril) compared to patients receiving an

ARB plus placebo[5]. The Center of Medications Safety has recommended that combination therapy with an ACEi and ARB should not be initiated in patients with diabetic nephropathy, diabetes and CKD; or non-diabetic kidney disease if being used for kidney outcomes. Similarly, an ACEi and an ARB should not be used concomitantly with aliskiren.

In this type II variation, the MAH proposed to update the SmPC for irbesartan-containing products in order to reflect contraindications and warnings of ARB use in combination with aliskiren. A brief bibliographic search including published results of the ALTITUDE trial (by Parving et al 2012; Parving et al 2009) and additional commentaries/reviews (Lillybland et al 2012; O'Brien et al 2007; Vaidyanathan S et al 2008; and Volpe et al 2012) has been provided, together with a company search of case report data of irbesartan/aliskiren.

The CHMP agreed with the proposal of including contraindications/warnings of dual RAAS blockade with irbesartan and aliskiren.

References:

1. Makani H, Bangalore S, Desouza KA, Shah A, Messerli FH. Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomized trials. BMJ. 2013 Jan 28;346:f360. doi: 10.1136/bmj.f360.

2. Catalá-López F, Macías Saint-Gerons D. Diabetes Mellitus and Risks of Dual Blockade of the Renin-angiotensin-aldosterone System. Rev Esp Cardiol. 2013 Feb 18. doi:pii: S0300-8932(13)00008-0. 10.1016/j.recesp.2012.11.010.

3. Susantitaphong P, Sewaralthahab K, Balk EM, Eiam-Ong S, Madias NE, Jaber BL. Efficacy and Safety of Combined vs. Single Renin-Angiotensin-Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis. Am J Hypertens. 2013 Mar;26(3):424-41. doi: 10.1093/ajh/hps038.

4. Mann JF, Anderson C, Gao P, Gerstein HC, Boehm M, Rydén L, Sleight P, Teo KK, Yusuf S; ONTARGET investigators. Dual inhibition of the renin-angiotensin system in high-risk diabetes and risk for stroke and other outcomes: results of the ONTARGET trial. J Hypertens. 2013 Feb;31(2):414-21. doi: 10.1097/HJH.0b013e32835bf7b0.

5. National PBM Bulletin, February 12 2013: Dual Renin-Angiotensin Adolsterone System Blockade in Diabetic Nephropathy and Increased Adverse Events. U.S. Department of Veterans Affairs Health Administration (VHA), Pharmacy Benefit Management Services (PBM), Medical Advisory Panel (MAP), and Center for Medication Safety (VA MEDSAFE). Available at: http://www.pbm.va.gov/vamedsafe/nationalpbmbulletin/DualRenin-AngiotensinAldosteroneSystemBlockadeandImpairedRenalFu.pdf

2.3. Changes to the Product Information

The MAH proposed the following changes to the Product Information (additions are underlined, and deletions are highlighted with ~~strikethrough~~), to which the CHMP agreed:

SmPC

Section 4.3 Contraindications

Do not co-administer Aprovel with aliskiren-containing medicines in patients with diabetes or with moderate to severe renal impairment (glomerular filtration rate (GFR) < 60 ml/min/1.73 m2).

Section 4.4 Special warnings and precautions for use

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

Dual blockade of the RAAS by combining Aprovel with aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function. The use of Aprovel in combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see section 4.5).

……

General: in patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with angiotensin converting enzyme inhibitors or angiotensin-II receptor antagonists that affect this system has been associated with acute hypotension, azotaemia, oliguria, or rarely acute renal failure (see section 4.5). As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke. (…)

Section 4.5 Interaction with other medicinal products and other forms of interaction

Aliskiren-containing products: the combination of Aprovel with aliskiren-containing medicinal products is contraindicated in patients with diabetes mellitus or moderate to severe renal impairment (GFR <60 ml/min/1.73 m²) and is not recommended in other patients.

Package Leaflet, Annex II and labelling

The Package Leaflet has been updated in accordance with the amendments to the SmPC. In addition, the MAH took the opportunity to align the annexes with the latest QRD template, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet. These changes are all acceptable.

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

After the CHMP review (EMA/CHMP/112042/2012) of the early termination of the ALTITUDE study with aliskiren, and the recommendations for inclusion of a contraindication of the concomitant use of aliskiren-containing medicines with ACEi and ARBs, the MAH has now submitted a type II variation to reflect these changes in the product information of irbesartan- and irbesartan hydrochlorothiazide-containing medicinal products. The amended sections of the Summary of Product Characteristics (SmPC) are 4.3 "Contraindications", 4.4 " Special warnings and precautions for use" and 4.5 "Interaction with other medicinal products and other forms of interaction".

These updates of the product information proposed by the MAH are in line with the changes to the aliskiren PI implemented as part of the recent referral procedure and were considered acceptable by the CHMP

The Package Leaflet has been updated in accordance with the amendments to the SmPC. In addition, the MAH took the opportunity to align the annexes with the latest QRD template, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet.

The CHMP considers that the variation application for the proposed changes to the SmPC, Annex II, labelling and Package Leaflet is approvable. The benefit-risk balance for the irbesartan-containing medicinal products remains positive.

Furthermore, the CHMP considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

This variation concerns a new contraindication related to concomitant use of angiotensin receptor antagonists - including irbesartan - with aliskiren in patients with diabetes mellitus or renal impairment as discussed in section 2.3 above.

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 changes:

Variations requested		**Type**
C.I.3.b	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	II

Update of SmPC sections 4.3, 4.4 and 4.5 to reflect that the concomitant use of Angiotensin II Receptor Blockers (ARBs) with aliskiren is contraindicated in patients with renal impairment and in patients with diabetes mellitus. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to align the annexes with the latest QRD template, to make editorial changes in the annexes and to introduce the contact details of the local representative in Croatia in the Package Leaflet.

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

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

Not applicable.