



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## Assessment report for Art 5(3) procedure: Angiotensin II (type-1) receptor antagonists and risk of cancer

Procedure no: EMEA/H/A-5(3)/1274

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



## 1. Background information on the procedure

On 24 June 2010 the Italian Medicines Agency (AIFA) requested the CHMP, in accordance with Article 5(3) of Regulation (EC) No 726/2004, to give an opinion on questions regarding a potential increased risk of cancer with angiotensin receptor blockers (ARBs) following the results of a meta-analysis of randomised controlled clinical trials investigating various cancer outcomes associated with ARB use which was published by Lancet Oncology. The publication in June 2010 by Sipahi<sup>1</sup> *et al* from the University Hospitals Case Medical Centre in Cleveland, Ohio, stated that there was a modest and statistically significant increased risk of new cancer occurrence in patients treated with ARBs, in particular a statistically significant increase in the occurrence of new lung cancers.

## 2. Scientific discussion

### 2.1. Introduction

Angiotensin II (AII) receptor antagonists (also known as angiotensin receptor blockers (ARBs) or AT<sub>1</sub>-receptor (AT1R) antagonists) constitute a therapeutic group which modulates the renin-angiotensin-aldosterone system (RAAS). Their main use is in the treatment of patients with hypertension. ARBs are also authorised in other indications, such as the treatment of chronic heart failure, recent acute myocardial infarction (MI), renal disease in type 2 diabetes mellitus, and the prevention of cardiovascular cerebrovascular diseases. ARBs have been available in Europe since the mid-1990s. The following ARBs are authorised in the EU: *candesartan*, *eprosartan*, *irbesartan*, *losartan*, *olmesartan*, *valsartan* and *telmisartan*.

ARBs were developed with the main aim to offer the potential to improve clinical outcomes for patients with heart failure beyond those seen with ACE-inhibitor (ACE-I), as well as providing an alternative for patients with previous intolerance of ACE-I.

Comparative studies in heart failure have failed to show non-inferiority compared to ACE-inhibitors and clinical guidelines recommend their use only and solely in those patients in whom ACE-inhibitors are contraindicated. There is also debate on whether ARBs have a tendency to increase MI. At present, the Summary of Product Characteristics (SmPC) for the ARBs have a warning that, as with all antihypertensive drugs, profound hypotension in patients with ischemic cardiomyopathy or ischemic cerebrovascular disease could result in MI or stroke.

The question of carcinogenicity of antihypertensive agents is a long-standing issue and there are numerous publications discussing possible causation due to ACE-inhibitors, calcium channel blockers and diuretics. Experimental studies reported an involvement of the renin-angiotensin system, particularly angiotensin II type-1 and type-2 receptors (AT1R and AT2R), in the regulation of cellular proliferation, angiogenesis, and tumour progression. In 2002, the LIFE study showed an increase in the occurrence of cancer associated with losartan in comparison with atenolol.

In 2003, a parallel randomised controlled trial, the "*Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity*" (CHARM) program, assessing ARBs in 7,601 patients with heart failure randomly assigned candesartan (n=3,803, titrated to 32 mg once daily) or matching placebo (n=3,796), reported after a median follow-up of 37.7 months, an unexpected finding of significantly

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<sup>1</sup> Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC. *Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol.* 2010 Jul;11(7):627-36.

higher fatal cancers in the candesartan group than in the placebo group (2.3% vs. 1.6%,  $p=0.038$ ). Following this report, the risk of cancer has been more thoroughly monitored in trials with ARBs.

Despite a significant overlap in the trials included, in the last three years two meta-analyses have been published, suggesting a potential signal of cancer risk associated with the use of ARBs.

In 2008 a network meta-analysis indicated that, when compared with placebo/untreated controls, the five major antihypertensive drug classes reported the following odds for developing cancer: 0.99 (0.80–1.24) for ACE-inhibitors; 1.12 (0.87–1.47) for ARBs; 1.00 (0.78–1.32) for beta-adrenergic blockers; 0.94 (0.73–1.19) for diuretics and 0.95 (0.79–1.13) for calcium channel blockers.

In 2010 the results of a meta-analysis of randomized controlled trials of ARBs conducted by Sipahi *et al* was published, showing that there was a modest and statistically significant increased risk of new cancer occurrence in patients treated with ARBs. In particular, there was a statistically significant increase in the occurrence of new lung cancers in ARB-treated patients. As a result, the Italian Medicines Agency, AIFA requested the CHMP to initiate a review on the potential risk of cancer with the use of ARBs. The questions addressed by the CHMP are discussed below.

## **2.2. Discussion**

### **What is the strength of the evidence generated by the Sipahi et al meta-analysis and is it consistent with signals from previous studies and/or meta-analyses?**

It is noted that following the results from the LIFE and CHARM trials, Regulatory Agencies have requested the monitoring of the occurrence of new cancers in all studies with ARBs conducted for regulatory purposes. Therefore, the majority of studies reporting cancer as an end point or as an event are those conducted for regulatory purposes.

Trials with a median follow-up of less than 12 months, or involving study population of fewer than 100 patients were excluded by the meta-analysis of 2,057 reports identified. 60 full-text publications met the inclusion criteria and were further examined for retrieving cancer data. The data were available for five of them: LIFE, TROPHY and TRANSCEND reported cancer occurrence; CHARM-Overall and OPTIMAAL reported cancer deaths. An online search for additional data led to two more trials reporting new cancer information, five trials reporting common types of solid-organ cancers, and six more trials reporting cancer death. Overall, nine trials were included into the analysis. For the primary objective of assessing the effect of ARBs on new cancer occurrence, a total of five trials were included: LIFE, TROPHY, TRANSCEND, ONTARGET, and PROFESS ( $n=61,590$ ).

For the secondary outcome of assessing occurrence of specific solid-organ cancers, five trials were included: LIFE, CHARM-Overall, TRANSCEND, ONTARGET, and PROFESS ( $n=68,402$ ). For the secondary outcome of assessing cancer-related deaths, eight trials were included: LIFE, CHARM-Overall, TRANSCEND, ONTARGET, PROFESS, OPTIMAAL, VALIANT, and VAL-HEFT ( $n=93,515$ ).

To assess for publication bias a funnel plot was generated. The test statistic for Begg's rank correlation method, Kendall's tau, was non-significant ( $p>0.80$ ) for new cancer occurrence and cancer death, denoting no evidence of publication bias.

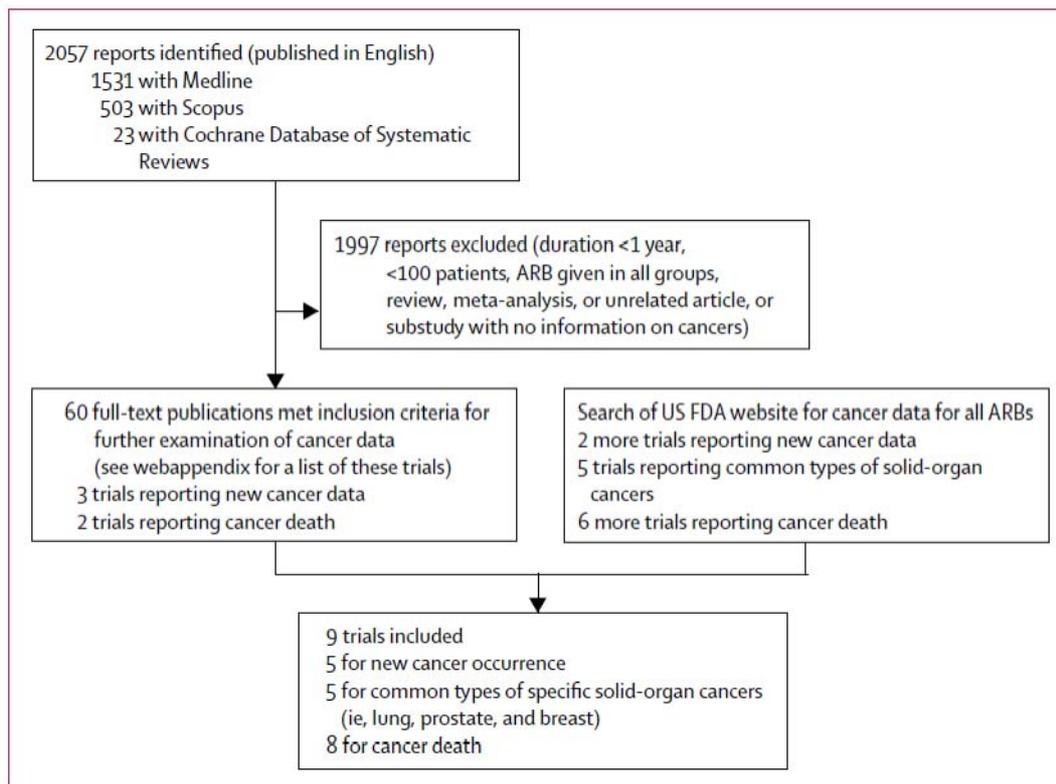


Figure 1 – Flow diagram of literature search to identify randomised controlled trials of angiotensin-receptor blockers (Sipahi et al, 2010)

From the 60 full-text publications meeting the inclusion criteria, 5 were selected for this meta-analysis because they provided information on cancer outcomes. Further trials were also identified from the FDA website. In total, 9 trials were included (see Figure 1). Such evidence highlights the potential for publication bias. The authors used a funnel-plot (a scatter plot of treatment effect against a measure of study size) analysis and did not find a significant heterogeneity. The tests for publication bias probably lack power such that the possibility of publication bias cannot be excluded (the funnel plot notably has no small negative studies in the bottom left of the triangle). In fact, in this particular context the potential publication bias might be due to the lack of information rather than to the lower sample size of the studies not included in the analysis (because not statistically significant). The exclusion of some large trials such as the VALUE (n=15,245) due to the fact that the study did not collect prospectively information on cancer is particularly relevant. One additional limitation not mentioned by the authors is statistical multiplicity i.e. many tests are performed without an apparent pre-specified primary end-point.

The authors provided in the web appendix the list of eligible publications that were not included in the analysis because of lack of information. Further effort should have been done by the authors to retrieve from the database any single eligible trial (>12 months of follow-up; >100 patients) with information on cancer outcomes.

Cancer was a pre-specified endpoint of special interest in three of the five trials that included new-cancer data for analysis of cancer occurrence (LIFE, ONTARGET, and TRANSCEND), corresponding to 66% (40,739 of 61,590) of patients with new-cancer data. Cancer was a pre-specified adverse event of special interest in the LIFE trial, and adverse events were monitored throughout the study and specifically recorded at each visit. In the ONTARGET and TRANSCEND trials, information on the occurrence of malignancies was also collected prospectively, in more detail than usual for trials of cardiovascular outcome. In the remaining two trials (PROFESS and TROPHY; 34% of patients [20,851

of 61,590]), cancer information was collected as new serious adverse events by per routine pharmacovigilance monitoring.

Since adequate monitoring of cancer risk was performed only in long term event studies initiated after the CHARM study, it is possible that the cancer risk might have been underestimated in most short-medium term studies and in those started before the publication of the CHARM program results.

The lack of standardised case definition and ascertainment procedures for assessing new cancer occurrence might therefore have biased the results in favour of an under-reporting of new cancer. The authors dealt with such potential bias by performing a sensitivity analysis, which included only those trials where such information was validated by an adjudication committee (ONTARGET, TRASCEND) or because it was a pre-specified adverse event of special interest (LIFE) (see Figure 2 below; analysis B). The results indicate an increase in the risk estimate from an HR of 1.08 (analysis A) to an HR of 1.11 (analysis B).

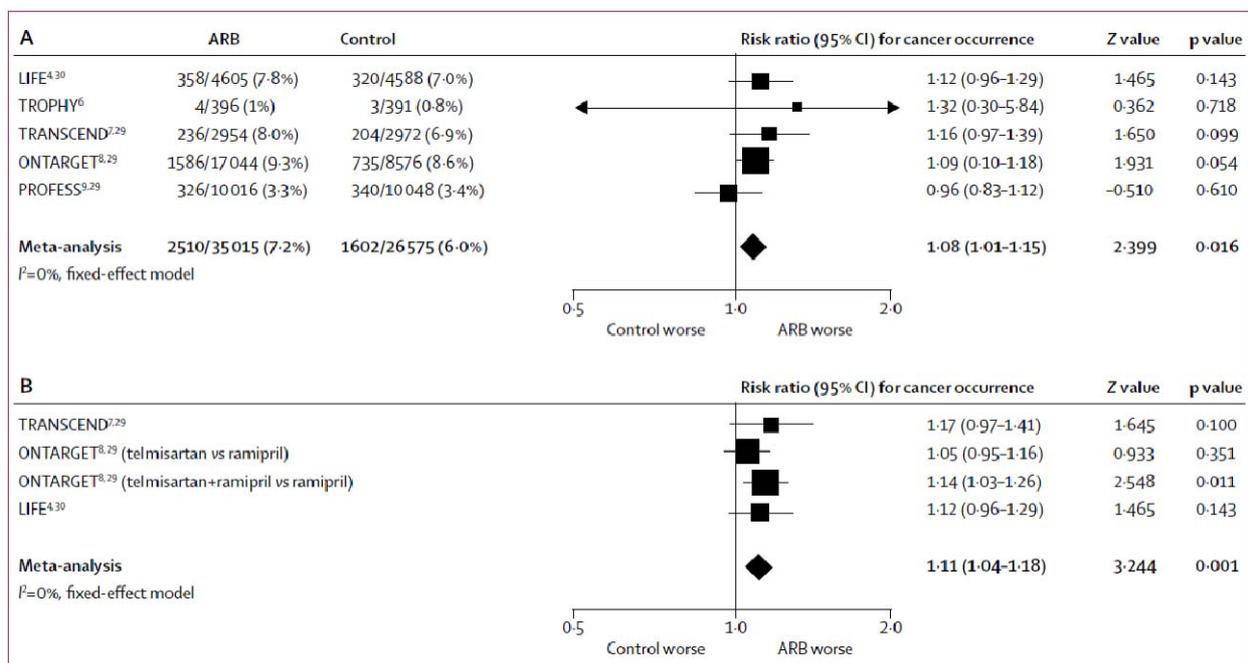


Figure 2 – Cancer occurrence reported in all included trials of angiotensin-receptor blockers (A) and trials in which cancer was a pre-specified endpoint (B) (Sipahi et al, 2010)

### Baseline cancer risk

According to the authors, there was no notable imbalance within trial groups with regard to age, sex, ethnic origin, smoking status, and history of previous cancer. Cancer history was obtained from 3 out of 9 trials, whereas smoking status was obtained from 5 out of 9 trials. Regarding cancer history, an imbalance was noted in the CHARM-Overall trials with a higher prevalence of cancer in the candesartan group, compared with placebo (7.1% vs. 6.4%). Overall, the results from these single trials showed a statistically non-significant increased risk for lung cancer (HR: 1.24; 95% CI: 0.73-2.09), prostate cancer (HR: 1.17; 95% CI: 0.70-1.95), and breast cancer (HR: 1.02; 95% CI: 0.52-2.00), whereas for cancer deaths a significant increased risk was observed (HR: 1.42; 95% CI: 1.02-1.98).

Since the selected trials were not designed to primarily assess the cancer endpoint, there is lack of relevant information about cancer risk at baseline (only available for 3 of the 9 studies analysed). Such data are necessary to provide unbiased results from the single trials included into the meta-analysis, because they contribute to the pooled results either in terms of risk estimate or in terms of statistical

significance. The importance of obtaining data on baseline cancer risk has been clearly confirmed. Firstly, the telmisartan brand leader conducted multi-factorial analyses using patient level data from ONTARGET and TRASCEND. In ONTARGET, smoking status (current and former), baseline lung malignancy, and age were the significant predictors of on-treatment onset of lung malignancies. In TRASCEND, smoking status (current and former) and age were significantly associated with lung malignancies. The treatment group was not found to be a predictor of lung malignancies in both trials. Secondly, results from the meta-analysis showed that the CHARM-Overall trial, where a higher prevalence of baseline cancer history has been reported in the candesartan group, is the only study reporting a significant increased association between ARB and cancer death. This evidence may be relevant, given that this study appears to drive the overall finding of a higher incidence of cancer death in ARB-treated patients (see Figure 3 below).

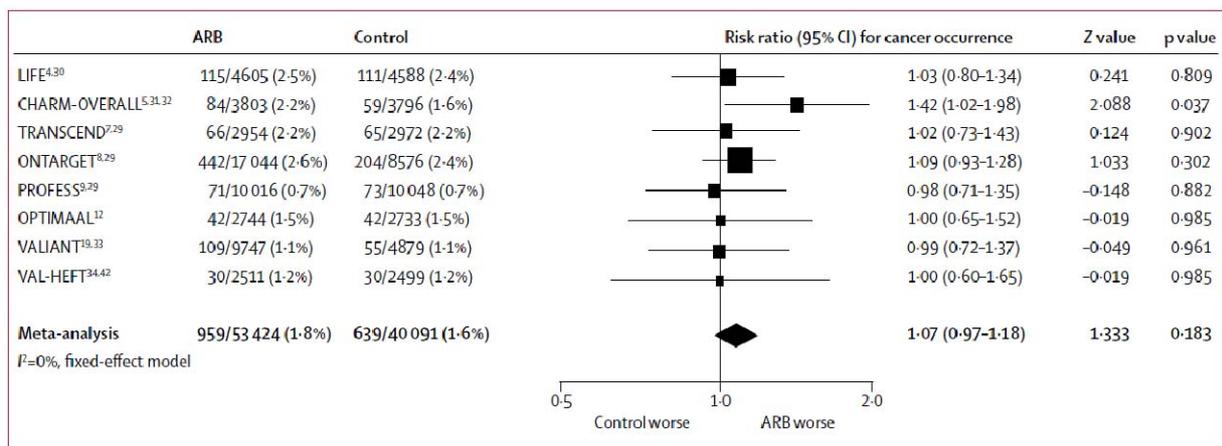


Figure 3 – Cancer deaths reported in randomised controlled trials of angiotensin-receptor blockers (Sipahi *et al*, 2010)

Finally, age, sex, smoking status, and cancer history cannot explain all cancer risk. For example, infection or inflammations of the prostate (prostatitis), in particular infection with the sexually transmitted infections chlamydia, gonorrhoea, or syphilis, seems to increase risk of prostate cancer, as well as obesity and elevated blood levels of testosterone. In addition, with regard to smoking, the study only records a yes/no response, whereas more detailed information on the extent of smoking (e.g. number of pack years) would give more accurate information on the risk of lung cancer.

However, it must be noted that because of the large sample size and the randomised design of the study, an imbalance in risk factors for cancer is unlikely.

### Results

The results of the Sipahi *et al* meta-analysis showed an increased risk of new cancer occurrence among patients receiving ARBs as compared to controls (RR 1.08, 95% CI 1.01–1.15). For the primary outcome of cancer occurrence, telmisartan was the main ARB used as the study drug (in 30,014 [85.7%] patients). The analysis of the 3 trials of telmisartan showed an increased risk in new cancers occurrence (RR 1.07, 95% CI 1.00–1.14; *p*=0.05). Interpretation of the meta-analysis is however complicated by the variety of comparator groups joined together (placebo, beta-blocker or ACE-inhibitor) and concurrent use of ARBs with ACE-inhibitors (ACE-I) in the ONTARGET, representing 32.5% of the total population included into the meta-analysis.

Indeed, the consistency of risk estimates were mainly based on pooled groups “ARB/ACE-I plus ARB alone” from the ONTARGET trial. Results from the assessment show that when only patients receiving ARBs were included, risk effects did not reach statistical significance.

The meta-analysis authors stated that: *“the analysis of cancer data was based on summaries of events from peer-reviewed publications or publicly disclosed documents, and the lack of availability of individual data and timing of cancers did not allow a more statistically powerful time-to-event analysis that could be useful for cancer because of the latency period.”*

The CHMP agrees with the authors’ statement. A patient level analysis has been performed by the MAH in ONTARGET, TRASCEND and PROFESS, although in this latest trial, malignancy status was not available at baseline and the outcome was detected as a serious adverse event without a specific validation.

For the primary endpoint ONTARGET, with 25,620 enrolled patients, represents 41.6% of the total population included in the meta-analysis. During 4.7 mean years of follow-up malignancies were recorded in 2,321 randomised patients (9.1%). The HR for new cancer occurrence was significantly increased for telmisartan/ramipril group vs. ramipril [1.14 (1.03-1.26)], regardless of cancer history at baseline, whereas a non significant increased risk has been reported when telmisartan/ramipril was compared with telmisartan [1.09 (0.99-1.21)]. When telmisartan was compared with ramipril, non-significant results were also reported [1.05 (0.94-1.16)]. However, assuming the ARBs-specific causal association with cancer, we would have expected risk estimates closer to relative effect of 1 for the comparison telmisartan/ramipril vs. telmisartan, and a significant increased risk for telmisartan vs. ramipril. Therefore, the results do not provide consistent evidence of causal association, unless a synergistic effect from the combination telmisartan/ramipril on target receptors promoting cell proliferation is hypothesised.

For the primary endpoint TRASCEND, with 5,926 enrolled patients, represents 9.6% of the total population included in the meta-analysis. During 4.7 mean years of follow-up malignancies were recorded in 440 randomised patients (7.4%). For this trial 2,954 patients were randomised to telmisartan and 2,972 to placebo. The HR for new cancer occurrence was not significantly increased for telmisartan vs. placebo [1.17 (0.97-1.41)], regardless of cancer history. However, a significantly increased cancer risk was reported when patients with baseline cancer history were excluded from the analysis [1.24 (1.01-1.52)].

For the primary endpoint PROFESS, with 20,332 enrolled patients, represents 33% of total population included in the meta-analysis. During 2.5 mean years of follow-up malignancies were recorded in 666 randomised patients (3.3%). For this trial 10,016 patients were randomised to telmisartan and 10,048 to placebo. The HR for new cancer occurrence was lower for telmisartan vs. placebo [0.92 (0.79-1.05)].

There was an excess of new lung cancers in all trials, with a significant excess in the LIFE trial (RR, 2.41; 95% CI, 1.23 to 4.71; p=0.01). The meta-analysis showed an increase in relative risk for the occurrence of new lung cancer in patients randomised to an ARB compared with control (RR, 1.25 (1.05 to 1.49); p=0.01]). This effect was also seen in the subgroup of patients who received background ACE-inhibitor (RR, 1.32 (1.03 to 1.69); p=0.031), but not among those not receiving a concomitant ACE-inhibitors (RR, 1.50 (0.93 to 2.41); p=0.097). In all five trials included, there was an excess of prostate cancer in the ARB groups compared with control, although it was not significant in meta-analysis (RR, 1.15 (0.99–1.34); p=0.076).

Overall, there was no significant difference in cancer deaths between patients randomised to ARBs and those randomised to control for the duration of follow-up (1.8% vs. 1.6%; RR, 1.07; 95% CI, 0.97–1.18; p=0.18). Among the eight trials included, only CHARM-Overall reported a significant increased risk. According to the authors, the absence of cancer death does not necessarily reject the hypothesis of an association because oncogenesis, tumour growth, and treatment failure followed by death is typically a slow process. Indeed, in trials with an average follow-up shorter than 3 years (PROFESS,

OPTIMAAL, VALIANT, and VAL-HEFT), the point estimate of RR for cancer death was very close to 1.0, and in trials longer than 3 years (LIFE, CHARM-Overall, TRANSCEND, and ONTARGET) the point estimate was consistently above 1.0.

In summary, the analysis of ARBs and lung cancer risk must be interpreted with caution. Five randomised controlled trials were included: LIFE, CHARM-Overall, TRANSCEND, ONTARGET, and PROFESS. Only three of them (CHARM-Overall, ONTARGET and TRANSCEND) reported baseline information on smoking status, a well recognised risk factor for lung cancer. In multifactorial analyses conducted by the MAH of telmisartan using patient level data from ONTARGET and TRANSCEND smoking status (current and former) was a significant predictor of lung malignancies in both trials, whereas the treatment group did not reach any statistical significance. In CHARM-Overall the proportion of smokers at baseline was higher in the candesartan group than in the placebo group.

Data on prostate cancer, although not statistically significant also deserve attention. In all randomised controlled trials included, an increased risk was reported. Indeed, this result seems consistent with the results of a recent pharmacoepidemiological study conducted in a Danish cohort (Pasternak *et al*, 2011) where ARBs were found to be associated with cancer of male genital organs (RR, 1.15; 95% CI, 1.02 to 1.28). However, when adjusted for multiple testing, statistical significance was not reached. Indeed, in this study the risk of prostate cancer did not increase with increased exposure, thereby rejecting the biological plausibility of this association.

For cancer death the same consideration highlighted for new cancer occurrence and solid cancer should be applied. In particular, the presence of different comparators in the control groups, the lack of relevant baseline information, the lack of patient level information which would permit to perform time-to-event analyses do not allow to draw any conclusion which might discard or confirm the results. The authors' comment about the point estimate of RR for cancer death indicating a greater risk of cancer death in studies with longer follow-up cannot be directly applied to the cancer death endpoint and need to be substantiated with further analyses.

### *Conclusions*

This meta-analysis suggests a small increased risk of new cancer occurrence associated with ARBs. However, unlike previous randomised studies (CHARM), it shows no evidence of an association with cancer death. The potential for publication bias, although intrinsic to this type of analysis, the lack of relevant information on baseline cancer risk, and the inconsistent results from the individual level analyses conducted in three of the five trials used for new cancer occurrence endpoint (83.9% of total population) do not allow any conclusions about the risk of cancer associated with ARBs.

In summary, the CHMP concluded that the evidence generated by the meta-analysis by Sipahi *et al* with respect to a putative association of ARBs with cancer risk is limited.

### **Does a biological plausibility exist and what could be the mechanism(s) of action of ARBs on cancer development? Might this be relevant to other related drug classes?**

The CHMP review considered whether a biological plausibility exists for an association between ARBs and cancer and if so whether the risk is a class effect or whether it is restricted to telmisartan.

A review of the pharmacology of ARBs demonstrates that there are clear differences across the class in terms of structure, affinity, biological half life and the nature of the angiotensin type 1 receptor (AT1R) antagonism. Telmisartan has a number of distinguishing features in terms of its pharmacology since it is a non tetrazole derivative but also because of its high lipophilicity, which results in an extremely long

half life and a high volume of distribution. This property explains the ability of telmisartan to concentrate within cells and may provide a basis for additional clinical actions compared with other ARBs at the same dose. Despite pharmacological differences, all ARBs have the common action of efficiently and specifically blocking the AT1R. However, significant variability does exist across the class in terms of the extent of the AT1R independent effects. As a result, pro-carcinogenic effects have been considered in terms of both AT1R-dependent and AT1R-independent effects.

The AT1R is expressed and up-regulated in a range of human malignant tissues and in addition many tumours have been demonstrated to express several components of the Renin-Angiotensin System (RAS), suggestive of a local RAS system. Stimulation of the AT1R has been known for many years to result in proliferative, inflammatory angiogenic and fibrotic effects and as such there is a wealth of compelling evidence to suggest that blockade of the AT1R would have beneficial effects on tumour development and progression. Pre-clinical studies have demonstrated anti-tumour effects both *in vivo* and *in vitro* against a range of different cancer cells and in a number of different experimental models. Consequently, blockade of the AT1R is being muted as a possible target for anti-tumour therapy and there is no data which would support the hypothesis that blockade of the AT1R *per se* would increase the risk of cancer.

However, the RAS system is a highly complex, interacting system with multiple opportunities for cross communication and as a result blockade of the AT1R has a number of other consequences which includes the un-opposed angiotensin type 2 receptor (AT2R), the increased production of Ang(1-7), a peptide which has been demonstrated to have hypotensive activity and other Ang peptides and, the increased production of plasma renin, Angiotensin II (AII) an octapeptide produced by the cleavage of the inactive decapeptide angiotensin I (AI) and angiotensin converting enzyme (ACE) levels. Nevertheless, both stimulation of the AT2R by AII and of the G protein-coupled Mas-receptor by Ang(1-7) is generally thought to oppose the action of AT1R stimulation and as such be antiproliferative, anti-angiogenic and apoptotic.

Some isolated studies suggest that under some conditions AT2R stimulation may contribute to AT1R effects but these studies are mostly in the context of cardiac hypertrophy in murine transgenic models of AT1R knockout. The relevance of this to blockade of the AT1R with an ARB is unclear. A further consequence of AT1R blockade is substantial increases in renin levels which have been shown to persist for at least one year. A receptor for prorenin/renin has been identified but its distribution and signalling pathways are unclear. However renin has been identified in a number of cancer cells and current studies would suggest that inhibition of renin is antiproliferative. This raises the possibility that increased renin activity, as a result of AT1R blockade, may stimulate proliferation in some cell types.

ARBs have a number of actions that cannot simply be explained in terms of AT1R blockade and this CHMP review highlights the variability of these effects across the class and in addition the lack of data to explain the mechanistic basis for some of the effects. In terms of AT1R independent effects, telmisartan is distinguished by its unique ability within the ARB class to stimulate the peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) at clinically relevant concentrations. In contrast to the thiazolideinediones (TZDs) which are full agonists at the PPAR $\gamma$  receptor, telmisartan is a partial agonist and therefore produces a different gene expression profile.

PPAR $\gamma$  has been proposed to play an important role in regulating cellular proliferation and differentiation and hence PPAR $\gamma$  signalling has been linked to an anti-tumour activity. However recent data suggests that the antiproliferative action of PPAR $\gamma$  agonists may in fact be independent of the PPAR $\gamma$ . It can not be ruled out that the ability of telmisartan to stimulate the PPAR $\gamma$  receptor may in some cells stimulate proliferation.

Other AT1R independent effects on oxidative stress, TXA<sub>2</sub> receptors and uric acid metabolism would be predicted to be anti-proliferative while effects on  $\beta$ -amyloid accumulation are unlikely to influence the progression of cancer.

In conclusion, the majority of data, obtained in systems where the Renin Angiotensin Aldosterone system (RAAS) is not activated and therefore not directly applicable to the scenario of hypertensive patients, does not support the hypothesis that ARBs would increase the risk of cancer at therapeutic doses and moreover there is no clear biological mechanism. Differences across the class are apparent in terms of AT1R independent effects but these effects largely also support an antiproliferative, anti-tumour effect. There is however some doubt with regard to the proliferative effect of PPAR $\gamma$  agonists at low concentrations and this has relevance for telmisartan, the only ARB able to stimulate the PPAR $\gamma$  receptor at clinically relevant concentrations. However, cancer risk was similarly reported for ARBs with and without PPAR $\gamma$  agonist activity and therefore this mechanism of action is unlikely. Further work is required in this area to clarify the balance between pro and anti proliferative effects following stimulation of this receptor. In particular, studies in systems where RAAS is activated, which would provide more detailed insights into the carcinogenic risk of ARBs compared to data generated to date, are lacking. Studies in systems where RAAS is activated would be of particular importance as the increased incidence of cancer has been reported in patients with conditions where this system is active and where the AT1R blockade may lead to a possible consequent AT2R stimulation.

#### *Conclusions*

In conclusion, the majority of the data, generated in systems not applicable to patients with activated renin angiotensin aldosterone system and therefore not relevant for the assessment of cancer risk, do not support the hypothesis that ARBs would increase the risk of cancer at therapeutic doses and moreover there is no clear biological mechanism. Differences across the class are apparent in terms of AT1R independent effects but these effects largely also support an antiproliferative, antitumor effect. There is however some doubt with regard to the proliferative effect of PPAR $\alpha$  agonists at low concentrations and this has relevance for telmisartan, the only ARB able to stimulate the PPAR $\alpha$  receptor at clinically relevant concentrations. However, cancer risk was similarly reported for ARBs with and without PPAR $\alpha$  agonist activity and therefore this mechanism of action is unlikely.

Studies in systems where the Renin Angiotensin Aldosterone system is activated are likely to provide more insight into the carcinogenic risk of ARBs as the suggested mechanism of a possible AT2R stimulation consequent to AT1R blockade is likely to occur in patients with activated Renin Angiotensin Aldosterone System which are those where the increased cancer risk has been reported.

Further work in this area would clarify the balance between pro and anti proliferative effects following stimulation of this receptor.

#### **Is this effect limited to telmisartan or should it be considered a class effect?**

Although most of the data included in the meta-analysis by Sipahi *et al* come from studies on telmisartan, as this was the drug studied in a greater number of patients in clinical trials, studies with losartan and candesartan have previously shown an increased risk of cancer and/or an increased mortality due to cancer (LIFE and CHARM studies). In addition, it is difficult to identify a different mechanism of action, specific to telmisartan that would support a selective susceptibility of telmisartan in inducing the occurrence of new cancers.

As per current knowledge, there are no differences in the properties and mechanisms of action between ARBs that would explain a different role on cancer. In addition, no selective susceptibility of telmisartan in inducing new cancers has emerged from clinical studies.

**What other non-clinical and clinical data (clinical trial or epidemiological data) are available publicly, and how could they impact this assessment?**

There are few epidemiological publications available which clearly address a possible association between ARBs and an increased risk of cancer. The available data consists of 5 cohort studies, 2 case-control studies and one meta-analysis. One case series was also identified.

Two publications looked at the increased risk of all cancer types (Coleman *et al*, 2008, Assimes *et al*, 2008) and 6 look at the effects of ARBs on breast (Fryzek *et al*, 2006), lung (Wilop *et al*, 2009), keratinocyte (Christian *et al*, 2008, Moscarelli *et al*, 2010), melanoma (Koomen *et al*, 2009) and renal cell cancer (Fryzek *et al*, 2005). None of the studies provide data on the effects of individual ARBs on cancer occurrence. Over half of the studies analyse the effects of ARBs together with ACE-inhibitors.

The study of antihypertensive use in renal cell cancer (RCC) found an increased risk of RCC among users of antihypertensives in general compared with non-users (RR 1.6, 95% CI 1.3 – 1.9). However, the risk for exclusive use of any class of antihypertensive including ARBs was not significantly elevated and the association was reduced to null after 5 or more years of follow-up. The authors contend that early-stage pre-diagnostic renal tumours may themselves lead to hypertension and that the observed association likely reflects protopathic bias.

The single meta-analysis identified (Coleman *et al*, 2008) reports that, across 27 trials evaluated, 3 of the groups (ACE-I, diuretics, calcium channel blockers) had an odds ratio (OR) slightly below 1.0 for cancer risk; beta blockers had an OR of 1.0 and ARBs were slightly above 1.0, although none of these findings were statistically significant. The trial populations were notably heterogeneous.

Many of these studies are limited by the small numbers of patients receiving ARBs in whom risk can be specifically calculated; the ARB patients have been subsumed into a larger group with ACE-inhibitor users. The 2 studies looking broadly at increased cancer risk show no statistically significant evidence of an association. Of the remainder, one study shows an increased risk of renal cell cancer for use of antihypertensives in general, not significantly associated with a specific class of antihypertensive. This is likely due to confounding. The study in lung cancer shows a 3.1 month longer median survival in patients receiving ACE-inhibitor/ARB (11.7 vs. 8.6 months, HR = 0.56, P = 0.03) but this work has notable limitations. The six outstanding studies show neutral results.

The bulk of the remaining published literature comes from in vitro studies seeking to show that ARBs may be anti-angiogenic and therefore retard cancer growth. Several publications in prostate cancer suggest beneficial effects.

Since the Sipahi *et al* meta-analysis was published, three further meta-analyses investigating a possible signal for ARBs and cancer have become available (Bangalore *et al.*, 2011; ARB Trialists Collaboration, 2011 and the FDA statistical review, 2011). These analyses include most of the available randomised controlled trial data and, although all three were conducted very differently, they all had very similar findings. None suggest an association of concern and, with an upper 95% CI of 1.06 for overall cancer, seem to exclude a risk as far as is likely to be possible for this kind of issue. These findings are largely supported by the two observational studies that have also been conducted (Pasternak *et al.*, 2011, Chang *et al.*, 2011). Some of the subgroup analyses and individual trials

demonstrated a modest increase or decrease in risk; however, these were not consistent across trials or analyses and are likely due to chance.

The new data are robust, provide a great deal of new information and can be considered to largely supersede previous evidence. Instead of supporting the original concerns raised for ARBs, the new data strengthen the view that there is no association between the use of ARBs and an increased risk of cancer.

### *Conclusions*

A search of the published literature for studies addressing the possible risk of cancer associated with the use of ARBs concluded the following:

(i.) There are few epidemiological publications available which clearly address a possible association between ARBs and increased risk of cancer

(ii.) The bulk of the published literature comes from *in vitro* studies seeking to show that ARBs may be anti-angiogenic and therefore retard cancer growth.

(iii.) Five cohort studies, 2 case-control studies, one meta-analysis and one case series were identified.

(iv.) None of the studies provide data on the effects of individual ARBs on cancer occurrence.

(v.) Over half of the studies analyse the effects of ARBs together with ACE-inhibitors.

Of the 8 studies evaluated, one shows a possible increase in occurrence of renal cell carcinoma with use of antihypertensives more broadly, one shows a possible decrease in lung cancer progression with ACE-inhibitor or ARB use and 6 studies show neutral results.

In conclusion, the analysis of the results showed that there is no robust evidence to support the findings of the recent Sipahi *et al* meta-analysis. On the basis of the currently available data, no association between the use of ARBs and cancer was identified.

### **Is it possible to identify factors associated with a risk of cancer in patients receiving ARBs?**

Patients with cardiovascular disease as well as those with increased cardiovascular risk share most risk factors with patients at increased risk of cancer. Indeed along with hypertension, diabetes, obesity, and cigarette smoking, ageing, diet and physical inactivity are all associated with both cardiovascular disease and cancer. In addition, concomitant ACE-inhibitor use, renal failure and ethnicity have also been associated with an increased cancer risk.

### *Hypertension*

Several studies have suggested a relationship between arterial hypertension and an increased risk of cancer. High blood pressure is associated with an increased risk of lung cancer in male hypertensive smokers.

Other studies have suggested a link between arterial hypertension and risk of breast, prostate, renal and colorectal neoplasia. It has been observed that patients with arterial hypertension have an increased risk of mortality from cancer and a reduced overall survival. However, it is not established, at present, whether hypertension *per se* is an independent risk factor for the development of cancer.

Possible mediators of the increased angiogenesis and progression of cancer are nitric oxide and activation of the renin-angiotensin-aldosterone system. Nitric oxide (NO) has an important

pathophysiological role in both hypertension and cancer. NO enables or enhances angiogenesis. Angiogenic growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) induce NO and require NO to elicit an effect. NO modifies the release of cytokines from macrophages. Furthermore, there is clear evidence of abnormalities in pulmonary NO levels of patients with lung cancer and primary pulmonary hypertension. Endothelial nitric oxide synthase (eNOS), a NO-generating enzyme, is expressed in vascular endothelium, airway epithelium, and certain other cell types and may be induced by several cardioactive drugs.

The other mediator that may link hypertension and cancer is the renin-angiotensin system. Renin releases angiotensin I from angiotensinogen which subsequently gets converted to the biologically active angiotensin II by the angiotensin-converting enzyme (ACE) in the lung. The role of the renin-angiotensin system in tumour angiogenesis is little understood. Most of studies evaluating the relationship between ARBs and cancer were performed either in isolated preparations or in animal models where RAAS was not activated (not hypertensive animals).

Angiotensin II (ATII) is implicated in the development of hypertension and exerts its actions through AT1R and AT2R receptors. Both AT1R and the AT2R receptors have been shown to stimulate angiogenesis. ATII induces VEGF, thereby playing an important role in VEGF-mediated tumour development and angiogenesis.

Although AT1 receptor antagonists may reduce neointima formation it has been suggested that the decrease in AT2 receptor gene expression associated with RAAS activation might enhance the AT1 receptor activation-induced ATII proangiogenic effect. Therefore an overstimulation of AT2 receptor may, partially overcome AT1 receptor blockade by ARBs and elicit a pro-carcinogenic effect. Evidence shows that both AT1R blockade with an ARB (which is associated with unopposed AT2R stimulation) and direct stimulation of AT2R are capable of stimulating tumour angiogenesis *in vivo*.

#### *Diabetes*

Growing evidence indicates that insulin resistance, a metabolic complication of obesity, may promote not only type 2 diabetes but also cancer. Epidemiological studies have shown that chronic hyperinsulinaemia and hyperglycaemia are associated with several types of cancer, and the relationship persists after controlling for BMI. Insulin influences cell growth and inflammation in several ways. It promotes the production of insulin-like growth factor (IGF-1) and in laboratory studies, insulin and IGF-1 stimulate cell proliferation and inhibit apoptosis (programmed cell death).

Adipose tissue is also an important source of inflammatory mediators, free fatty acids and other metabolically active products known as adipokines, which include leptin, tumour necrosis factor alpha, interleukin 6, and adiponectin. Inflammation is associated with cancer risk, possibly by generating reactive oxygen species that could damage DNA.

#### *Cigarette smoking*

The effect of current and past cigarette smoking on the development of cancer is well known. Cigarette smoking increases the risk not only of lung cancer but also of other types of cancer such as oesophageal, stomach and bladder tumours. The TRASCEND study reported an association between cigarette smoking and lung cancer, however no association between telmisartan and an increased risk of cancer was shown.

#### *Obesity*

Obese patients have an increased likelihood of developing cancer and of dying from it. The causes for the increased occurrence of cancer in obese patients are likely to be similar to those listed for hypertension and diabetes.

### *Ethnicity*

Different ethnicities have different susceptibilities to different types of cancer. In ONTARGET/TRASCEND, an increased risk of cancer was observed in North and South America compared to Europe and Asia, suggesting that ethnicity and environmental factors may play a pathogenetic role in the development of cancer.

### *Concomitant use of ACE-inhibitors*

In the ONTARGET study, patient level analyses reported an increased HR for new cancer occurrence for telmisartan/ramipril vs. ramipril [1.14 (1.03-1.26)], regardless of cancer history at baseline, whereas a non-significant increased risk was reported when telmisartan/ramipril was compared with telmisartan [1.09 (0.99-1.21)]. Such evidence has been confirmed in another network meta-analysis where a 14% increased risk for the combination was observed, thus suggesting a possible synergistic effect from the combination telmisartan/ramipril on target receptors promoting cell proliferation. However, the results from the meta-analysis were mostly obtained from ONTARGET, indeed follow-up is only around 2–5 years, which is too short to show an increase in cancer detection. Moreover, such combination is likely to be used in patients with severe hypertension, raising the possibility that high blood pressure itself is a risk factor for cancer at some sites.

### *Renal failure*

Chronic kidney disease (CKD) and cancer are connected in a number of ways: cancer can cause CKD either directly or indirectly through the adverse effects of therapies; CKD may, conversely, be a risk factor for cancer; and both may be associated because they share common risk factors, often toxins. Compared with the general population, kidney transplant recipients have a three- to four-fold increase in overall cancer risk, and relative risks higher than 3 for about 20 specific tumours, most, but not all, of which are known or suspected to be caused by viral agents. After dialysis, cancer risk increases 10% to 80% according to studies, with relative risks significantly higher than in the general population, for about 10 cancer sites. There is also emerging evidence of an excess risk of cancer in patients in early CKD stages.

### *Ageing*

The relationship between ageing and cancer is rather conflicting. Typical features of the age-pattern of overall cancer incidence rate overall include an increasing rate until around 80 years and a decline afterwards. Two kinds of mechanisms have been suggested to explain the increase in cancer risk with age. The first explanation refers to simple dose-duration effects of carcinogenic exposures, regardless of any effects of aging. Another explanation implies that individual vulnerability to cancer increases with age, in particular disturbance of hormonal balance, an increase in the number of loci of chronic proliferation, and the decline in immune surveillance with age. On the other hand, there are some biological mechanisms, as well as some epidemiological issues which might suggest a decline in cancer risk with old age. Firstly, the detection bias related to the restriction of screening procedures of older individuals; secondly, the depletion of susceptible individuals due to selection throughout the life of individuals less prone to cancer; thirdly, age-related decline in cell proliferation rate may suppress cancer development.

### *Diet*

Diet and cancer are associated. While it is not yet possible to provide quantitative estimates of the overall risks, it has been estimated that 35 percent of cancer deaths may be related to dietary factors. Almost all cancers (80-90%) are caused by environmental factors, and of these, 30-40% of cancers are directly linked to the diet. It has been suggested that eating mostly foods of plant origin and aiming to meet nutritional needs through diet alone, while limiting consumption of energy-dense foods,

red meat, alcoholic drinks and salt and avoiding sugary drinks, processed meat and mouldy cereals or pulses is likely to decrease cancer risk.

#### *Physical inactivity*

Evidence is accumulating that high levels of physical activity are associated with a reduced risk of some cancers. This evidence is most consistent for colon cancer, which is reduced by 40–50 % among the most active individuals, compared with the least active. The effect is evident in men and women, and appears to be independent of important confounding factors. However, there may be important interactions with body fat levels; a high BMI has been reported to be associated with an increased risk of colon cancer in sedentary men but not in physically-active men. Whilst the evidence for breast cancer is less consistent, case-control studies typically suggest a reduction of 25–30 % among the most active women, although several studies have found no effect. Potential mechanisms include systemic influences and others relevant only to site-specific cancers. One unifying hypothesis is that physical inactivity reduces insulin sensitivity, leading to a growth promotional environment which may facilitate neoplasm. The non-specific immune system may be improved by physical activity, possibly through the summative effects of repeated exercise bouts. Regular exercise, even at a recreational level, probably reduces exposure to estrogens and thus decreases the risk of breast cancer. Increased colonic peristalsis, and thus reduced bowel transit time, might partly explain the lower risk of colon cancer in active people.

#### *Conclusions*

The CHMP noted that an increased risk of cancer can be linked to multiple factors, including the ones described above (hypertension, diabetes, smoking, obesity, ethnicity, renal failure, Concomitant use of ACE-inhibitors, ageing, diet or physical activity) and therefore considered that the lack of complete baseline clinical characteristics of individual patients enrolled in the studies included in the Sipahi *et al* meta-analysis does not allow a sound evaluation of whether the population of patients with cancer in the different studies had different clinical characteristics of baseline risk or peculiar clusterings of risk factors that could suggest an increased susceptibility to specific types of cancer.

The authors specifically pointed out that the lack of patient level data does not allow estimating the effect of sex, age, and smoking on the main results.

The importance of obtaining data on baseline cancer risk has been clearly confirmed by three different evidences. First, the multifactorial analyses conducted by the MAH of telmisartan using patients level data from ONTARGET and TRASCEND, where smoking status (current and former), baseline lung malignancy, and age were the significant predictors of on-treatment onset of lung malignancies. Second, results from the meta-analysis showed that the CHARM-Overall trial, where a higher prevalence of baseline cancer history has been reported in the candesartan group, is the only study reporting a significant increased association between ARB and cancer death. Finally, different cancer event rates reported in the randomised controlled trials included in the Sipahi *et al* meta-analysis may suggest that without a careful collection of all relevant information at patient level it will not be possible to disclose or exclude a potential association.

#### **If observed, is the signal identified for lung cancers only or also for other types of cancers?**

Of all specific solid organ cancers examined in the Sipahi *et al* meta-analysis, only new lung cancer occurrence was significantly higher in patients randomly assigned to receive ARBs than in control patients (0.9% vs. 0.7%, RR 1.25, 1.05–1.49; p=0.01). Lung cancer encompasses a variety of distinct

clinical entity with different histopathologic features and often with specific molecular signatures. The classification of cancers detected merely based on the organ in which they originated therefore seems of limited use and does not allow any speculation or further interpretation. More detailed information about the histopathology of the cancers would have been helpful and should have been collected.

In a more recent meta-analysis of antihypertensive drugs and risk of cancer (Bangalore *et al*, 2011), no significant association between ARBs and cancer was detected. In this review, an increased risk for the combination of ARBs and ACE-inhibitors could not be ruled out but unfortunately, cancer specific analysis were not undertaken because of the scarcity of data in each trial.

There are therefore several limitations that do not allow to draw any conclusion about the role of ARBs in the development of cancer and even more limitations exist regarding the possibility to identify signals for specific types of cancer.

As a matter of fact, cancer was a pre-specified outcome in very few trials and therefore, under-reporting is likely to have occurred in most cases. Furthermore, the data provided to date are mostly missing relevant information such as histopathology and molecular features and, at best, the cancers detected are classified according to the site of origin.

Furthermore, the median follow-up in the clinical trials was too short (3-5 years) to adequately detect the impact of these drugs on the development of cancer, which results in a consistent lack of information about the risk of cancer with ARBs, even when taking into consideration the fact that antihypertensive drugs are usually administered for decades.

The potential mechanisms of action of ARBs on cancer development are unclear. Although a biological plausibility could support the identification of the lung as a potential selective target of ARB-induced tumours, this evidence is not confirmed by data from non-clinical, clinical and epidemiological studies.

#### *Conclusion*

On the basis of the available data, it is not possible to confirm the conclusions of a selective increase in the number of new lung cancers, as reported in the Sipahi *et al* meta-analysis.

### **Does the data on cancer alone or together with other signals lead to a need to revise the SPC or to amend or implement Risk Management Plans?**

The Sipahi *et al* meta-analysis provides weak evidence of a small increase in the risk of new cancer occurrence associated with ARBs. Unlike previous randomised studies (CHARM), the meta-analysis shows no evidence of an association with cancer death.

Both nonclinical and clinical studies available in the literature, although not always appropriately designed to detect the risk of new cancer occurrence, do not provide further evidence in support of a causal link between ARB treatment and cancer occurrence.

Although a clear biological mechanism cannot be identified from studies on isolated organs or systems or in animals where RAAS is not activated, the evidence would suggest that blockade of the AT1R receptor would have beneficial effects on tumour development and progression. Differences across the ARB class are apparent in terms of AT1R independent effects. Among ARBs, telmisartan is distinguished by its ability to stimulate the PPAR $\gamma$  receptor at clinically relevant concentrations.

Overall nonclinical and clinical studies do not provide evidence of differences in the properties and mechanisms of action between ARBs that would explain a different role on cancer. In addition, no

selective susceptibility of telmisartan in inducing the occurrence of new cancers has emerged from clinical studies. However, uncertainty remains on the possibility that antagonism at PPAR $\gamma$ , might be relevant in the modulation of cell cycle and be directly or indirectly involved in the generation of new cancers.

It is considered that present evidence from clinical trials and epidemiological studies do not warrant any change of the Summary of Product Characteristics (SmPCs) of ARBs with regard to the risk of cancer.

### 3. Overall Conclusion

The CHMP reviewed the Sipahi *et al* meta-analysis and concluded that the weak evidence of a small increase in the risk of new cancer occurrence associated with ARBs is limited by several bias.

The signal identified in the Sipahi *et al* meta-analysis was not confirmed, neither by the trial-level meta-analyses of randomised clinical trials conducted to evaluate the risk of incident (new) cancer in patients taking ARBs compared to patients taking non-ARB treatments (FDA statistical review, 2011, Bangalore *et al*, 2011, ARB Trialist Collaboration, 2011), nor by the findings of two observational studies that have been recently published (Pasternak *et al*, 2011 and Chang *et al*, 2011). Some of the subgroup analyses and individual trials demonstrated a modest increase or decrease of risk, but no consistency across trials was observed.

Taking into consideration that antihypertensive drugs are usually administered for decades, the median follow-up in clinical trials is too short (3-5 years) to adequately detect the impact of ARBs on the development of cancer and this results in a consistent lack of information on the risk of cancer with ARBs in most of the published clinical trials.

The majority of the reviewed epidemiological studies showed neutral results and although suffering from limitations, were generally not supportive of a signal.

Pre-clinical studies, although not designed to mirror the condition of basal RAAS activation that is characteristic of hypertensive patients, do not provide a clear biological mechanism to support the hypothesis of an increased risk of cancer with ARBs.

Differences across the ARB class are apparent in terms of AT1R independent effects. Among ARBs, telmisartan is distinguished by its ability to stimulate the PPAR $\gamma$  receptor at clinically relevant concentrations. At present, there is no clear biological evidence to support differences in the mechanism of cancer development with specific ARBs solely on the basis on the PPAR $\gamma$  activity.

However, uncertainty remains on the possibility that antagonism at PPAR $\gamma$ , might be relevant in the modulation of cell cycle and be directly or indirectly involved in the generation of new cancers.

The CHMP concluded that the current evidence from clinical trials and epidemiological studies do not support a signal of increased cancer risk associated with ARBs, and was therefore of the opinion that no changes to the Summary of product characteristics (SmPC) of ARBs are required with regard to the risk of cancer. However, the CHMP also concluded that it will be important that all ARBs will continue to be monitored via routine pharmacovigilance activities with regards to the risk of cancer.

The CHMP noted that some MAH are currently already closely monitoring the occurrence of cancer cases, reviewing these cases as part of the Periodic Safety Update Reports. In addition, the CHMP also noted that some MAHs have initiated further epidemiological studies, investigating the relationship of ARBs and the occurrence of cancer.

## 4. Overall conclusions

The Committee considered the procedure under Article 5(3) of Regulation (EC) No 726/2004 initiated by the Italian Medicines Agency (AIFA) to investigate the possible association between the use of angiotensin receptor blockers (ARBs) and an increased risk of cancer.

The Committee considered relevant expertise, data available in the literature in relation to angiotensin receptor blockers and various cancer outcomes associated with ARB use.

The CHMP concluded that the currently available evidence does not confirm a meaningful increased risk of cancer with the use of Angiotensin II (type-1) receptor antagonists.

The Committee was of the opinion that no changes to the Product Information of the ARB products are currently needed. ARBs will continue to be monitored via routine pharmacovigilance activities with regards to the risk of cancer.

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