Annex

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Overall summary of the scientific evaluation of Kynamro

- Quality issues

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of opinion, there are no outstanding issues on the quality of the active substance or the medicinal product.

- Efficacy issues

Treatment with mipomersen results in a statistically significant decline of 24.7% and 35.9% in LDL-C levels at Primary Efficacy Time point (PET) versus baseline in patients with homozygous familial hypercholesterolaemia (HoFH) and severe heterozygous familial hypercholesterolaemia (HeFH) on top of statins, respectively. This corresponds to a reduction by 21% and 48% with mipomersen when corrected with placebo (for HoFH and HeFH, respectively). In absolute terms, it corresponds to a placebo-corrected reduction with mipomersen by -100 and -114 mg/dl in LDL-C at PET versus baseline, which may be considered of clinical relevance. Approximately 70% of patients in the mipomersen groups of pivotal trials had at least a 15% decrease in LDL-C levels from baseline to PET in comparison with approximately 20% of patients in the placebo groups. Statistically significant percent reductions with mipomersen compared to placebo were also observed for apo B, TC, and non HDL-C from baseline to PET. However, based on data from pivotal studies and OLE CS6 study, withdrawal rates may be as high as 50%-70% at two years and mainly due to mipomersen treatment intolerability, thus, significantly decreasing the rate of patients that may benefit from the lipid-lowering effect of the drug in the long-term, which is considered a major concern. In the HoFH, the retention rate was only 8% at 3 years, with 63% withdrawing due to adverse events.

Uncertainties remain regarding effects of mipomersen on long-term cardiovascular outcome. Potential negative effects on cardiovascular risk factors may counteract the potential beneficial effect on CV outcome due to reduction in LDL-C.

- Safety issues

The mipomersen safety database from the conducted clinical programme is limited considering the original target population that intends to include patients with HeFH, even if it is limited to severe cases, and raises serious safety concerns for the both patient groups. For a medicinal product that is intended to protect patients at high CV risk, the data on Major Adverse Cardiac Event (MACE) during the phase 3 studies raise a safety concern. Mipomersen reduces LDL level in a relevant manner, but in long term use might induce other changes in CV risk factors that could counteract such effect.

Mipomersen exhibits adverse effect on liver and other mechanisms of liver damage beyond fat accumulation cannot be excluded. Importantly, steatosis is plausibly correlated with the effect on cholesterol levels, which introduces an additional doubt on the long-term sustainability of this therapy, particularly in those patients where

the beneficial effect in the lipid profile is more marked. There is no known threshold at which hepatic steatosis or liver fat fraction results in inflammation and progressive liver disease, which renders the monitoring of onset of liver related adverse events difficult.

The numerically higher number of neoplasms and cancer raises an additional safety concern. There is no proven relationship between mipomersen treatment and the occurrence of neoplasm, mainly due to the low incidence rate, lack of systematic evaluation during the studies, and the short timing after start of mipomersen, but uncertainties about the clinical relevance of these findings remain. Mipomersen is also associated with a high incidence of flu-like symptoms, effect on inflammatory markers and decrease on complement component C3. Mipomersen may be immunogenic and antibodies were detected in 65% of subjects taking the product. In addition, complement activation was more pronounced in patients with antibody formation. However, the consequences of these findings are unclear.

Therefore, the CHMP concluded on 13 December 2012 that the benefit/risk ratio of mipomersen is negative.

Following the CHMP scientific conclusions adopted on 13 December 2012 that Kynamro was not approvable for the treatment of

Kynamro is an apolipoprotein B (apo B) synthesis inhibitor indicated as an adjunct to maximally tolerated lipid-lowering medicines and diet to reduce low density lipoprotein-cholesterol (LDL-C) in adult patients with homozygous familial hypercholesterolaemia (HoFH).

On the basis of the following grounds for the refusal of the Marketing Authorisation:

The long-term benefit/risk of mipomersen remains undetermined, even if the indication is restricted to patients with HoFH.

- CHMP ground 1: The long-term consequences of mipomersen-induced liver steatosis are of major concern and difficult to monitor in clinical practice through non-invasive tests;
- CHMP ground 2: Uncertainties remain regarding effects of mipomersen on long-term cardiovascular outcome. In particular, the numerical imbalance in overall CV events, MACE and CV hospitalisations is of concern. Potential negative effects, in particular inflammatory effects, immunological reactivity, increase in blood pressure and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CV outcome due to reduction in LDL-C;
- CHMP ground 3: The high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a major concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in a less selected population in standard practice;

on 31 January 2013, the applicant submitted its detailed grounds for the request for re-examination of the CHMP opinion recommending the refusal of the granting of the marketing authorisation.

Summary of the applicant's grounds for re-examination:

The applicant requested a re-examination of the CHMP's opinion for mipomersen, to re-assess the benefit/risk in the very rare Homozygous Familial Hypercholesterolaemia (HoFH) population (estimated size in the European Union, 500 patients) with a high unmet medical need. The applicant addressed the CHMP's concerns of liver and cardiovascular safety, tolerability and patient retention, as well as post-approval management plans, in light of the benefit/risk in the HoFH population, which the applicant believes is positive.

The indication originally proposed in the mipomersen MAA included both HoFH and severe HeFH. Following discussions at the Scientific Advisory Group (SAG) meeting in September 2012, the applicant restricted the indication to HoFH patients only, in which the lifetime exposure to extremely high low density lipoprotein cholesterol (LDL-C) levels is responsible for CVS morbidity and early age mortality. The benefits of mipomersen-induced reductions in LDL-C in this population, which is at great risk of premature death, are anticipated to be large (potentially greater than 50% risk reduction of CHD, based on meta-analysis of multiple clinical trials), in contrast to the known and hypothetical risks of treatment with mipomersen.

The following issues were addressed by the applicant;

- A statistically significant mean reduction in LDL-C of approximately 25% (absolute change -2.92mmol/L) in patients with HoFH already receiving maximally tolerated lipid-lowering therapy is highly relevant for this small group of patients with a high unmet medical need;

- Effects of mipomersen on the liver (including increases in hepatic transaminases and hepatic fat) decrease or stabilize with continued treatment in most patients and return towards baseline when patients discontinue mipomersen treatment. The applicant presents a comprehensive approach to risk management for liver effects, including hepatic transaminase monitoring, liver imaging to assess hepatic fat, and observations of clinical signs/symptoms of possible liver damage.

- Within the context of the small number of patients tested, the 6-month treatment time of placebo-controlled studies, and the 6-month follow-up time, final conclusions regarding CVS adverse effects as demonstrated in the clinical studies cannot be reached at this time; however, the results of analyses performed to date do not provide support for a difference in the rate of MACE between treatment groups. Additional data will be collected in on-going and proposed studies.

- The rates of discontinuation from mipomersen treatment (taking into account the patient's consented length of treatment) are similar to those observed with statins and other lipid-lowering therapies and with other approved SC injectable therapies studied in similar long-term studies, although, due to a lack of placebo control in the long-term extension study, the true adherence rate in this study is not possible to assess. The applicant has proposed a Patient Support Programme (a broad adherence support programme) to help address this concern. While some patients might discontinue, patients remaining long-term are anticipated to receive benefit from substantial reductions in LDL-C.

The applicant presented an updated proposed SmPC and RMP, and the post-authorisation safety study (PASS) and believes that mipomersen would serve as an important therapeutic option to help address the significant unmet medical need of

patients with HoFH.

The CHMP considered the following:

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the PRAC (PRAC meeting 4-7 February 2013) and the advisory expert group held on 12 March 2013.

CHMP position on ground 1

In the clinical development programme increases in hepatic transaminases (ALT, AST) and liver fat were observed frequently in patients who received mipomersen therapy.

Liver enzyme increase

With regard to ALT and AST elevations, results from the pooled phase 3 studies (mipomersen n=261, placebo n=129, including patients with HoFH and HeFH) are summarized. In the pooled phase 3 studies, thirty six (13.8%) mipomersen-treated patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry. For 14 (5.4%) of these patients, dosing with mipomersen was stopped (stopping rules were ≥8 x ULN for AST/ALT on one occasion, ≥5 x ULN for AST/ALT over 7 days, or ≥3 x ULN for AST/ALT and elevated bilirubin). Of the 22 patients in the mipomersen-group with ALT levels ≥ 3 x ULN, 19 experienced decreases in ALT levels below 3 x ULN during continued treatment. In the Open-Label Extention study, patients showed ALT increases (18%), AST increases (16%), hepatic enzyme increases (3%), abnormal liver function tests (2%), and transaminases increases (0.7%). Twenty two (15.6%) patients experienced increases in ALT and AST that met protocol-defined monitoring/safety rules for liver chemistry; for 8 (5.7%) of these patients, dosing with mipomersen was stopped.

The applicant claims that in the majority of patients ALT and AST levels stabilize or decrease even with continued treatment or they return to (near) baseline following discontinuation of mipomersen treatment. This may not be the case for all patients and for patients with sustained increase of ALT or AST level the risk in terms of hepatic damage still remains unclear. From the available data, it is also not clear whether patients´ ALT or AST levels reached a maximal effect (plateau). In all phase 3 studies, patients were excluded for “significant hepatic disease”. In case of the pivotal study in HoFH patients (ISIS 301012-CS5) patients with a documented history of hepatic disease, liver cirrhosis, or liver steatosis were also excluded. Exclusion criteria were also in place to ensure adequate hepatic function based on laboratory values (ALT, ALT > 1.5 x ULN).

Steatosis

The CHMP noted that in two phase 3 studies (ISIS 301012-CS7 and ISIS 301012-CS12) hepatic fat fraction was assessed with magnetic resonance imaging (MRI) at baseline and Week 28 (or early termination):

- a median increase in hepatic fat fraction of 9.6% in mipomersen treated patients versus 0.02% in placebo-treated patients was observed,
- 61.8% (63/102) of mipomersen treated patients with paired MRI studies experienced a ≥5% increase from baseline in hepatic fat.

In the OLE study, the number of patients with available data at baseline and week

26, week 52 and week 72 is too small to draw firm conclusions regarding long-term effects on liver fat accumulation with mipomersen treatment. In the pivotal study in HoFH patients (ISIS 301012-CS5), hepatic fat was not routinely measured post – baseline, however, according to the applicant, there were 11 patients from CS5 with liver fat content assessment at baseline and at 12 months or longer on mipomersen treatment.

There was an association between the higher increases in hepatic fat content and greater percent reductions in apo B consistent with the mipomersen mechanism of action, suggesting a direct relationship between the degree of mipomersen lipid-lowering effect and the degree of steatosis, which the CHMP considers to be a concern still not adequately addressed.

According to literature (e.g. as summarised in the AWMF guideline on the histopathology of non-alcoholic and alcoholic fatty liver disease; German Society of Pathology, 2009), the natural course of hepatic steatosis/non-alcoholic fatty liver disease (NAFLD) in individual patients is not predictable; it is indicated that steatosis may progress to steatohepatitis/NASH in about 10-20% of cases, and of these less than 5% ultimately develop cirrhosis. As liver biopsy was not performed on a regular basis in the mipomersen study programme, it is not clear whether a small or a significant proportion of patients with mipomersen-induced steatosis also had inflammatory changes and fibrosis, i.e. might develop steatohepatitis, which may not be reversible after stopping the treatment.

Thus, the CHMP concluded that with respect to mipomersen´s hepatotoxicity, no aspects other than the ones already assessed in the initial procedure, which could lead to different conclusions, were presented by the applicant. Mipomersen treatment can cause liver enzyme elevations and hepatic steatosis and this may induce steatohepatitis. There is a concern that this could progress to hepatic fibrosis and ultimately cirrhosis, over the course of several years still remained. Considering that liver fat accumulation correlates with its effects on LDL, this hepatic effect is likely to appear in virtually all patients in whom the drug is exerting a significant effect.

The crucial question is how to identify patients at particular risk of long term liver damage and whether persistent hepatotoxicity can evolve for some patients whose transaminases and increased liver fat fraction do not return to baseline after discontinuation of mipomersen treatment and who are thus at risk to develop progressive liver disease. Though such liver disease could develop after long-term treatment, and thus patients could have experienced CVS benefit, hepatotoxicity could also develop as sequel to liver enzyme elevations following only short term treatment, even if patients are discontinued early. These patients would not have experienced any CVS benefit. Mipomersen is a drug that is intended for life-long administration; therefore further long-term data on hepatic safety in HoFH patients are essential before marketing authorisation could be granted. The CHMP concluded that such data has not been presented by the applicant at this time point.

CHMP position on ground 2:

Retrospectively analysed CVS risk

The pivotal studies with mipomersen have neither been prospectively planned nor adjudicated for CVS safety outcome and thus, only limited conclusions can be drawn

from the presented data. This is regarded by the CHMP as a major deficiency, and was also criticized by the expert advisory group.

The adopted Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (CPMP/EWP/3020/03/2004), states on the matter that the safety database should be large enough to reasonably rule out any suspicion of a detrimental effect of the new drug on mortality and that this requirement acquires special relevance in case of drugs belonging to a new therapeutic class. Furthermore, the guideline also states that "a new lipid-modifying agent is only acceptable for authorisation if there is no suggestion of a detrimental effect on morbidity and mortality. Otherwise, additional studies to clarify the drug effect on these parameters are mandatory." The issue of prospective planning for CVS safety outcome is even more specifically addressed in the recent Draft Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (EMA/CHMP/718840/2012).

The CHMP acknowledged that in a small population like that of HoFH patients, the collection of a large database is not likely; nevertheless the importance of monitoring the CVS safety data as stressed in this guidance still applies. Therefore, the lack of predefined adjudication of CVS events is clearly a deficiency and, if a marked difference in CVS events is observed, this may raise a concern despite a small database.

Numerical imbalance in CVS events

Despite the fact that CVS events analyses were performed *post hoc*, the imbalance observed in the pivotal trials is worrisome. On the other hand, given the absence of events in the placebo arms of the combined pivotal phase 3 studies in patients at very high cardiovascular risk, the relatively small sample size and short study duration, this finding might also be attributed to a chance. This is based on the consideration that in a high risk population a larger proportion of events could be expected also in the placebo group. Indeed, an annual event rate of 6% has been described for a composite endpoint of non-fatal MI and cardiac death in a comparable population (Scandinavian-Simvastatin Survival Study Group, 1995, Lancet). A similar or even higher event rate might be expected for MACE (including acute myocardial infarction, stroke or CVA, unstable angina, PCI, and CABG) in a patient population such as the one enrolled in the pivotal phase 3 studies (HoFH and severe HeFH patients). Furthermore, in the placebo arm of the pooled phase 2 and 3 trial population including patients at somewhat lower CVS risk (as compared with the very high CV risk in HoFH patients), a higher number of MACE was noted, again potentially indicating that the absence of MACE in the placebo arms of the pivotal studies of overall small size might be a chance finding. Nevertheless, the relevance of the direct comparison to mipomersen within the two trials must not be disregarded.

Potential effect of LDL reduction

The applicant argues that the degree of LDL reduction observed with mipomersen treatment is expected to result in a potential reduction in coronary heart disease risk greater than 50%, which is based on meta-analyses of data from multiple studies (Baigent, 2010, the Lancet). The CHMP felt that this assumption would imply that the benefits of mipomersen treatment in HoFH patients would outweigh an unknown detrimental effect of this new substance. However, while it is agreed that the LDL reduction is predictive of a long-term CVS risk reduction, the implied magnitude of reduction of CHD risk of 50% is speculative. It cannot be taken for granted that the

proposed extrapolations apply, i.e. whether the observed LDL reduction in HoFH patients, starting from LDL levels at the upper end of the scale, will translate into equally large CVS risk reductions as claimed for statin treated broad hyperlipidaemic populations of different states of health. This view was also supported by the experts who considered the extrapolation as only hypothetical.

In addition, it must also be considered that the estimates result from a small HoFH patient set, and though a treatment effect on LDL reduction is shown, the magnitude of this estimate is still prone to some variability. Finally, LDL reduction is only one mechanism affecting cardiovascular risk and as discussed above, no detrimental effect should be present that might counteract such improvements.

To conclude on ground 2, the discussion provided by the applicant for the re-examination of Kynamro does not provide a new insight to the former CHMP assessment on mipomersen treatment and CVS risk. Clinical studies have not been prospectively planned nor adjudicated for CVS safety outcomes so that only limited conclusions can be drawn from the presented data. Though considerable uncertainty remains, overall the analyses suggest an unfavourable effect of mipomersen treatment on several CVS risk factors. The CHMP also noted that the experts were not reassured that mipomersen is not conclusively linked to renal and CVS harm, and concluded that a >50% reduction in 5-year CHD risk as envisaged by the applicant for mipomersen treatment is purely hypothetical. Furthermore, although the relevant risks (apart from the off label use) are identified within the RMP, the PRAC considers the RMP insufficient to adequately identify CVS risk. A detrimental effect of mipomersen on CVS risk has not been shown but cannot be excluded since data are too limited.

CHMP position on ground 3

Focusing on the targeted HoFH population, the CHMP noted that the withdrawal rate for HoFH patients who had been enrolled in the pivotal 6 months DB study CS5 and consented to further participate in the OL extension study CS6 (for one or two years, including the time in CS5), was approximately 60% (23/38) within the first two years. Withdrawal rate was similar in HoFH patients and in the full population of OLE CS6 (56%). Within (maximal) 2 years of treatment almost 50% (18/38) of these HoFH patients withdrew from treatment due to AEs, mainly due to injection site reactions (ISRs), flu-like symptoms (FLS) and liver enzyme elevations.

The withdrawal rate - even if “similar to that observed with statins and other lipid-lowering therapies and with other approved SC injectable therapies studied in similar long-term studies” as claimed by the applicant - must be seen in the context of the identified safety concerns and the limited population studied.

With respect to the Kynamro Patient Support programme, the CHMP considered that its usefulness, suitability and applicability in different EU countries are difficult to foresee.

With regard to ground 3, the CHMP concluded that the high withdrawal rate is not per se regarded as a sufficient reason to withhold approval of an effective treatment option in a population of very high CVS risk, but, on a population level, the low tolerability resulting in low treatment adherence will have a negative impact on the utility of a treatment intended for long-term/life-long use. For the individual patient, the worst case scenario could be that they might not obtain the potential benefit of

mipomersen in terms of reduced CVS morbidity/mortality because they cannot tolerate long-term treatment, but might be harmed by progressive liver disease resulting from mipomersen-induced steatohepatitis. Furthermore, the CHMP considered the input from the expert group meeting and noted that there was an agreement amongst the experts that the tolerability of mipomersen treatment was poor. The experts felt, however, that potentially a restricted prescription programme in dedicated centres capable of providing support on individual patient basis might be helpful.

As part of their discussions, the CHMP discussed whether a Marketing Authorisation under exceptional circumstances for Kynamro in the restricted claimed indication as presented by the applicant during the oral explanation could be considered. The CHMP concluded that such type of Marketing Authorisation could not be recommended in the present case as it does not fulfil the requirements of Article 14(8) of Regulation (EC) No 726/2004, in particular, as the applicant would be able to provide comprehensive data on the efficacy and safety under normal condition of use of Kynamro.

The CHMP also discussed whether a conditional Marketing Authorisation for the claimed restricted indication could be considered. This was not considered applicable either, even if possible within the scope of Article 2 of Commission Regulation (EC) No. 507/2006, as the requirements as defined in Article 4 of the said Regulation were not met, in particular the demonstration by the applicant of a positive risk-benefit balance of the medicinal product and the likelihood to provide comprehensive clinical data by way of specific obligations. Such conditional Marketing Authorisation could therefore not be recommended.

Overall, based on the assessment of the detailed grounds for re-examination submitted by the applicant, including the revised risk management proposals for monitoring of liver lipids and liver toxicity, and the revised restricted indication, as applied for by the applicant, the CHMP concluded that the benefit/risk of Kynamro remains unfavourable.

Grounds for refusal

Whereas

The long-term benefit/risk of mipomersen remains undetermined, even if the indication is restricted to patients with HoFH. Although most of the relevant risks are identified within the risk management plan, the risk management system is considered inadequate and the proposed risk minimization measures are deficient in a number of important areas. The studies proposed are poorly defined and it is questioned that these can solve the concerns of particular interest like CVS events/hepatic toxicity.

1. Uncertainties remain regarding effects of mipomersen on long-term cardiovascular outcome. In particular, the numerical imbalance in overall CVS events, MACE and CVS hospitalizations is of concern. Potential negative effects, in particular inflammatory effects, immunological and renal toxicity (as shown by proteinuria) on other cardiovascular risk factors may counteract the potential beneficial effect on CVS outcome due to reduction in LDL-C.
2. No conclusive evidence was provided to support the assumption that mipomersen-induced liver steatosis, which is associated with its mechanism of

action, has a benign course. Concern remains about the potential progression of fatty liver disease to steatohepatitis and fibrosis, for which monitoring of patients at risk of developing inflammatory and fibrotic changes includes repeated liver biopsy. Furthermore, there is a potential risk of irreversibility of liver disease even if mipomersen-treatment is stopped.

3. The high overall withdrawal rate with mipomersen after 2-3 years, even in the restricted HoFH population, remains a concern, thus severely limiting the number of patients that may obtain a potential benefit from its lipid-lowering effect. Given that withdrawals are mainly due to intolerance, it is unlikely that retention rates may be improved in clinical practice.

The CHMP is of the opinion that the safety and efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, pursuant to Article 12 of Regulation (EC) No 726/2004, the CHMP has recommended the refusal of the granting of the marketing authorisation for Kynamro.