SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of RILUTEK. This scientific discussion has been updated until 1 January 2004. For information on changes after this date please refer to module 8B.

1.   Introduction

Rilutek tablets contain riluzole, a new chemical entity of the benzothiazole class. Riluzole is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). The indication is based on data derived from two pivotal clinical trials in which it has been demonstrated that riluzole induces a modest extension of the life of patients with ALS regardless of the onset type. The claimed indication for this medicinal product is :"To extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS)".

ALS is a progressive degenerative disorder of motor neurons and motor cortex. The symptoms of ALS are characterised by a progressive and irreversible decrease of muscle strength. The following definition of the pathology of ALS is found in the Oxford Textbook of Medicine: "a disease in which degeneration affects motor neurons in the anterior horns of the grey matter of the spinal cord, in certain somatic motor nuclei of the cranial nerves and in the cerebral cortex. There is no inflammatory reaction and microscopy provides no clue to the cause of the initially asymmetrical but progressive neuronal loss. As both upper and lower neurons are affected to varying degrees in different patients, the symptomatology is diverse." The disease has an unremitting course of wasting and weakness and is usually fatal within three years.

Although the pathogenesis of ALS is not completely elucidated and no validated models exist in which riluzole may be tested, it is suggested that glutamate (the primary excitatory neurotransmitter in the central nervous system) plays a role for cell death in the disease. Riluzole is proposed to act by inhibiting glutamate processes. The mode of action is unclear.

2.   Part II: Chemical, pharmaceutical and biological aspects

The pharmaceutical data described in Part II of the dossier are summarised below.

Synthesis:

The synthesis route comprises 5 steps beginning with the nitration of the starting material trifluoromethoxybenzene. Control during the first three steps was by a GC method and the fourth and fifth steps by an HPLC (CN reverse phase) method. Satisfactory information has been provided on the in-process control methods and satisfactory specifications are shown to be applied for control of the intermediate products. Satisfactory specifications and details on the control tests implemented were provided for the materials contributing to the structure of the final molecule and for the other reactants, reagents and solvents.

The analytical methods employed (GC, TLC, HPLC) were found to be capable of controlling the drug substance within its design specification. Drug substance specification was controlled by testing appearance, identity, colour, melting point, particle size distribution, water content, appearance and colour of methanolic solution, sulphated ash, heavy metals and related substances assays.

Proof of structure was provided by elemental analysis, UV and IR spectroscopy, EI and CI mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. Satisfactory spectral interpretations have been provided and appear to be consistent with the proposed molecular structure.

The physicochemical attributes of the molecule are adequately presented. The parameters studied included solubility (in methanol, HCl and water), melting point, pK, partition coefficient and polymorphism. X-ray diffraction examination of 5 industrial batches showed no evidence of polymorphism.

A comprehensive study on potential impurities is presented. Impurities related to residual solvents, related substances arising from the synthesis (including intermediates and secondary reaction products), degradation products (monitored by stress testing; heat, light, acid, alkali and peroxide stress in organic and aqueous solutions) were addressed adequately. The drug substance was found to be extremely stable, with only two significant degradation products being observed when riluzole was in solution in acetone and exposed to light. Degradation impurities were not found in normal conditions. Batch analyses were performed on 24 batches of material, ranging in size from 300g to 55.6kg (production scale), used in preclinical and clinical studies. Stability data were generated on 6 batches of drug substance, 3 pilot and 3 production. No deviations from initial values for assay or related substances were observed. The data support the proposed storage period of 24 months before re-test. Real-time studies are on-going to confirm the stability of the active drug substance over 24 months.

Dosage form:

The core of each tablet contains 50 mg of active drug substance and the excipients, anhydrous dibasic calcium phosphate, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate and croscarmellose sodium. All the excipients used have been shown to comply with the most stringent pharmacopoeial requirements available, primarily with the European Pharmacopoeia.

The active drug substance was found to have local anaesthetic actions and this necessitated film coating the product. The core is film coated, comprising hydroxypropylmethylcellulose, polyethylene glycol 6000, titanium dioxide and purified water.

Three formulations are described. Initial manufacturing development centred around a water/alcohol/povidone wet granulation process (A) which produced a product for use in early clinical studies. Subsequently a move to direct compression formulations (B) based on dibasic calcium phosphate and microcrystalline cellulose was made and the third formulation is the marketing formulation (C), which is also produced by direct compression. The account of the qualitative and quantitative optimisation of the formulation selected for development appears convincing and the arguments put forward are sound. There was concern over the possible lack of clinical efficacy due to the differences in C_{max} of the formulations B and C in the dose ranging study 301; justification was based on the safety data collected with the 200mg dose in study 301.

Pilot scale batches were manufactured using different input batches of active drug substance and excipients to validate the robustness of the formulation process, to identify the critical process parameters and to determine appropriate in-process controls. Suitable controls were applied to the powder blend, the tablet cores and the coated tablets.

In vitro dissolution was not influenced by the particle size. Comparative *in vitro* dissolution profiles of 3 industrial scale batches (produced at the intended manufacturing site) and two development batches, demonstrated no significant differences in release characteristics.

Validation data were provided on 3 full-scale production batches. Full details are provided on blending conditions, batch identification of input material, compression and coating. Overall it is concluded that the manufacture is sufficiently robust to provide assurance that the process produces tablets of consistent quality complying with the design specification.

Finished product specification was controlled by testing appearance, colour, identification (HPLC, IR) and assay and related substances (HPLC) of riluzole, identification of titanium dioxide, uniformity of content, dissolution and microbiological quality. The total related substances limit is proposed not more than 0.8%, which is made up of synthetic impurities and potential degradation products.

Satisfactory batch analyses data were provided on 4 full-scale production batches manufactured at the intended production site.

Stability data were generated on 4 pilot batches and 3 production batches of tablets stored in the PVC/aluminium blisters intended for the marketed product. No significant changes from initial values were noted for production scale product stored under all storage conditions. Overall, the product exhibits a good stability profile and the data, as presented supports the proposed shelf life of 24 months. The shelf life was consequently extended to 36 months through a Type I variation. It was agreed that no special storage instructions should apply to Rilutek.

3. Part III: Toxico-pharmacological aspects

The preclinical dossier is extensive and complies with GLP standards except for some early studies, which have no major significance for the assessment.

Pharmacodynamics

Riluzole has been shown to cross the blood brain barrier and to be active in various in vivo experimental models of neuronal injury involving excitotoxic mechanisms such as cerebral ischemia. Riluzole *in vitro* protects cultured rat motorneurons from the excitotoxic effects of glutamic acid and prevents the death of cortical neurons induced by anoxia. In vitro and animal model studies have shown that riluzole is able to modify neurotransmission mediated by glutamate, particularly in circumstances where overstimulation of the post-synaptic nerve occurs.

Summarised below is a list of its activities (derived from the primary pharmacological studies) which led to the rationale for progressing this compound to clinical trials:

- Protection against neurotoxicity in rat brain slices exposed to depolarising agents acting at excitatory amino acid receptors.

- Protection against anoxia or glutamate toxicity in cultured motor neurones.

- Protection of rat cortical neurones against toxic factors in CSF from patients with ALS

It should be noted however that there were no validated animal models of ALS in which to test Riluzole.

Effects of riluzole unrelated to the desired use include muscle relaxation and sedation (through depression of CNS activity) in rodents, but not neuroleptic, anxiolytic or psychostimulating activity in usually sensitive models. At 2 mg/kg i.v and above, EEC and sleep patterns were found to be changed. Although the action of riluzole on voltage-dependent sodium channels may have consequences on cardiac function, no cardiovascular effects of significance were seen at 3 mg/kg in rats. The local anaesthetic action observed at > 1mM concentrations could be the result of riluzole's action at these ion channels. Riluzole showed no anticholinergic action and only transient effects on dog respiratory function at doses of 2 mg/kg and above.

Of the 7 metabolites examined, only 2 (the 5-hydroxy- and hydroxylamine compounds) retained some of the qualitative pharmacological properties of riluzole. No new interactions with receptor binding sites were found. The maximum concentrations of the metabolites were considered to be too low to be of importance.

Pharmacokinetics

Pharmacokinetics were studied in the mouse, rat, rabbit, monkey and dog.

The use of radiolabelled riluzole showed that absorption from the GI tract was efficient but variable in all species. A high oxidative hepatic metabolism was evidenced in all species, the elimination of metabolites occurring mainly through urinary tract. Distribution to body tissues was extensive, with CNS concentrating radioactivity some threefold over plasma level within 1 hour of a single dose. However, tissue retention was low and by 72 hours after dosing radioactivity was only significant in the organs associated with excretion, plus a small residuum bound to melanin. Repeated administration of radiolabelled riluzole identified thyroid, adrenals, and skin as retainers of concentrations higher than those of plasma for at least 7 days.

Radioactivity in rat foetuses and milk confirmed the wide distribution property of riluzole. However, kinetics in pregnant animals was not significantly different.

The formation of a ureido metabolite (RP 69597) in monkey (3%) and man (10%) is also mentioned in this dossier although no mention is made whether this metabolite might be a possible cause of adverse effects at levels of riluzole beyond that for the desired activity.

Possible interaction kinetics have been suggested for compounds such as amitryptiline, clomipramine, diazepam and diclofenac, but the in vitro inhibition constants for these substances indicate that in vivo interactions are unlikely to be of clinical importance.

©EMEA 2004

Toxicology

Single dose studies:

Acute toxicity was related to the CNS impact of riluzole. The dose-response relationship indicated a steep slope from mild lethargy, plus effects on respiration and CV function, to lethality.

Repeated administration studies:

In i.v or oral studies lasting from 14 days to 6 months, the clinical signs of toxicity were attributed to CNS reactions resulting from the excessive inhibition of the transmission processes, which were manifest as salivation and lack of co-ordination followed by sedation, lethargy, reduced activity, prostration and eventual mortality.

Reductions in red blood cell parameters and/or alterations in liver parameters without histology impairment were noted in subacute and chronic toxicity studies in rats and monkeys. In dogs haemolytic anaemia was observed.

In a single toxicity study, the absence of corpora lutea was noted at a higher incidence in the ovary of treated compared to control female rats. This isolated finding was not noted in any other study or species.

On the basis of toxicology studies, liver, blood and ovarian cells can be regarded as three potential target organs.

Reproductive toxicology:

Doses of 8 mg/kg/day had no adverse effects on reproduction and development in rats although at 15 mg/kg/day (which is higher than the recommended human dose), adverse effects including mortality, loss of implantation in survivors, reduced reproductive performance and fertility and toxicity in offspring during lactation were observed.

Teratogenicity tests:

Standard design teratogenicity tests showed no evidence that riluzole could cause malformation or malfunction in fetuses of rats or rabbits.

Conventional genotoxicity: *in vitro* assays; utilising rat liver S9 fraction to model metabolism, gave no evidence of genotoxic potential for riluzole. In vivo assays in rat and mouse also gave no indication of chromosomal damage. There remains the possibility that these models did not generate all metabolites relevant to humans, particularly since no metabolic characterisation of the S9 fraction was conducted.

Carcinogenic potential: Riluzole did not show any carcinogenicity potential in either rats or mice.

Special toxicity studies: Riluzole has been shown to induce haemolytic anaemia in dog. Various possible mechanisms of action have been investigated, but no alterations were found in different red blood cell parameters (electrolyte content, osmotic fragility etc.).

No haemolytic potential has been shown in vitro on human, monkey, rat and dog erythrocytes.

A bromo derivative, seen as a significant impurity, was not mutagenic in a standard Ames test and not more acutely toxic than riluzole in mice.

Exposure of the environment to Rilutek is not considered to be a concern as judged from the risk assessment supplied.

Post-authorisation toxico-pharmacological data

At the time of the initial submission in July 1995, RPR112512 (N-hydroxy-riluzole), described as the major active metabolite of riluzole, could not be measured *in vivo* due to chemical instability of RPR112512 during blood sampling/treatment and the lack of a sensitive analytical method. As appropriate analytical methods and sampling conditions for RPR112512 were defined, additional pharmacokinetic and metabolism studies were conducted to determine the exposure to RPR112512 in the previous preclinical toxicology studies as well as pharmacokinetic and toxicity studies including an extensive battery of genotoxicity assays.

It was concluded that there were no unexpected adverse findings, with the exception of chromosome damage induced by RPR112512 in the L5178Y cell line only. This is not considered to have any significant effect on the risk benefit ratio. All other data suggest RPR112512 presents no greater risk than that already known for riluzole. The MAH updated section 5.3 of Summary of Product Characteristics to include this new information through a Type II variation.

4.   Part IV: Clinical aspects

Tolerance and pharmacodynamics studies

Changes were recorded in the EEG spectrum, proving that Riluzole crosses the brain barrier. Although somnolence was the most common dose-dependent CNS side effect observed, Riluzole did not affect the sleep profile. No significant changes in the psychomotor performances were observed in studies carried out on 129 healthy volunteers involved in 7 studies except the vigilance, which was sometimes decreased at high doses.

In one study in healthy volunteers, therapeutic doses of riluzole reduced significantly the EEG alterations caused by hypobaric hypoxia simulating an altitude of 5000 m. In another study, riluzole had no effect on similar parameters measured in healthy volunteers in a model of hypoxia corresponding to an altitude of 6000 m. Riluzole has also been shown to moderately reduce the cerebral metabolism of glucose in some regions of the brain as shown by Pet-scan.

Pharmacokinetics studies

About 350 subjects were enrolled in 16 studies. In most of the studies Riluzole was given via the oral route of administration.

The pharmacokinetics of riluzole have been evaluated in healthy male volunteers after single oral administration of 25 to 300 mg and after multiple-dose oral administration of 25 to 100 mg bid. The pharmacokinetics of riluzole were also studied in healthy elderly, as well as in subjects with impaired renal or hepatic function. In healthy volunteers, plasma levels increase with the dose and the pharmacokinetic profile is dose-independent and shows a linear PK behavior.

With multiple dose administration (10 day-treatment at 50 mg riluzole bid), unchanged riluzole accumulates in plasma by about 2 fold and steady-state is reached in about 5 days.

Administering oral dosing of 25, 50 or 100 mg twice daily, the elimination half-life of riluzole ranges from 9-15 hours with a steady state plasma concentration being reached at 3-8 days. In clinical study 301 the clearance of riluzole remains stable over time up to month 10. No accumulation of the drug with time was observed.

Absorption

Riluzole is rapidly absorbed after oral administration with maximal plasma concentrations occurring within 60 to 90 minutes (Cmax = 173 ng/ml). About 90% of the dose is absorbed and the absolute bioavailability is 60%. The rate and extent of absorption is reduced when riluzole is administered with high-fat meals (decrease in Cmax of 44%, decrease in AUC of 17%).

Distribution

Riluzole is extensively distributed throughout the body and has been shown to cross the blood brain barrier. The volume of distribution of riluzole is about 245 l (3.4 l/kg). Riluzole is about 97% protein bound and it binds mainly to serum albumin and to lipoproteins.

Metabolism

Unchanged riluzole is the main component in plasma and is extensively metabolised by cytochrome P450, with subsequent glucuronidation. In vitro studies using human liver preparations demonstrated that cytochrome P450 1A2 is the principal isoenzyme involved in the metabolism of riluzole. The metabolites identified in urine are 3 phenolic derivatives, one ureido-derivative and unchanged riluzole. The pharmacokinetics and biological activity of the metabolites have not been investigated. About 20 metabolites of riluzole are found in urine.

Excretion

Less than 1% of riluzole is excreted unchanged. Most of the substance is converted to glucurono-conjugated derivatives (pathway through cytochrome P450 1A2 and UDPG-T)). The overall urinary excretion accounts for about 90% of the dose. Glucuronides accounted for more than 85% of the metabolites in the urine.

Special populations

The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole bid) were not affected in elderly healthy volunteers (> 70 years). Thus, there are no special instructions for the use of riluzole in this population.

There was no significant difference in pharmacokinetic parameters between patients with moderate or severe chronic renal insufficiency (creatinine clearance between 10 and 50 ml.min^{-1}) and healthy volunteers after a single oral dose of 50 mg riluzole. However, since repeated dose administration has not been studied in subjects with renal impairment, treatment of this population is not recommended.

The AUC of riluzole after a single oral dose of 50 mg, increased by about 1.7 fold or 3 fold in patients with mild chronic liver or moderate chronic liver insufficiency, respectively. Riluzole is contraindicated in patients who have hepatic disease or have baseline transaminases greater than 3 times the upper normal limit.

Efficacy studies

Three randomised controlled trials have been reported, referred to as trials 216, 301 and 302.

Two strata were defined a priori in the study designs: Amyotrophic Lateral Sclerosis (ALS) of limb or bulbar onset.

Trial 216 was the first trial and compared 100 mg of Rilutek with placebo; trial 301 was a dose-response trial comparing 3 doses with placebo and was considerably larger; trial 302 was a comparison of 100 mg with placebo in patients ineligible for trial 301. In the three studies, survival, defined by patients who were alive, or not intubated or not tracheotomised was the primary efficacy endpoint. Secondary end-points were functional scores (MRC, NORRIS).

In study 216, patients with Amyotrophic Lateral Sclerosis of bulbar onset survived longer on Rilutek whereas in study 301, the two Rilutek treated groups showed a marginally longer survival than placebo treated patients, and no effect on survival was shown in study 302. On this basis, taking also into consideration the absence of any evidence of efficacy on symptoms of the disease, concerns were expressed on the robustness of the conclusions derived from the statistical analyses and on their generalisation to the population of ALS patients to be treated with Rilutek.

Therefore an ad hoc experts group was called by the CPMP to discuss both statistical and clinical issues related to the interpretation of the clinical trials results. In preparation of this expert group meeting the Company was requested by the CPMP to answer some statistical questions on 20 October 1995 and the ad hoc working group met on 15 November 1995. A technical report summarising the status of methodological issues relating to efficacy of Rilutek was issued at request of the CPMP.

Study 216

This study was designed as multicentre, double blind, placebo-controlled, randomised, parallel group trial. 155 patients aged 19 to 75, were randomised to riluzole 100 mg/day (50 mg twice daily, 77 patients) or placebo (78 patients) and were followed-up for 12 to 21 months.

The ALS patients were stratified at entry into limb or bulbar onset form. Main exclusion criteria were: tracheotomy present or pending, dementia, vital capacity ratio <60%, significant renal or hepatic impairment. Patients who were pregnant, lactating or taking potentially hepatotoxic drugs were also excluded from the study.

The main efficacy endpoint was overall survival at one year. Secondary endpoints were changes from baseline in functional evaluation.

©EMEA 2004

In the primary analysis, survival was significantly prolonged for patients who received riluzole as compared to patients who received placebo (survival rates were 55.8% versus 48.70 % for riluzole and placebo, respectively; p value = 0.116 Logrank test; p value = 0.047 Wilcoxon test; p value = 0.08 Cox model). All other analyses reached the significance level whatever the cut-off date or the statistical test was. The effect was more pronounced in patients with bulbar onset form (increase in survival time of about 8 months in comparison with placebo treated patients). The enhanced efficacy amongst the bulbar stratum in comparison to the population with limbar onset was observed in the context of a sub-group analysis, and was not confirmed in later trials.

Overall, study 216 provided evidence of efficacy on survival: Nevertheless, no functional effect was evidenced.

Study 301

This study was designed as a multicentre, double blind, placebo-controlled, randomised, parallel group, dose ranging study.

Study 301 was a confirmatory trial comparing 3 doses of riluzole with placebo and was considerably larger than trial 216.

959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. The ALS patients were stratified at entry into limb or bulbar onset form. Main exclusion criteria were: tracheotomy present or pending, dementia, vital capacity ratio < 60%, significant renal or hepatic impairment. Also patients pregnant, lactating or taking potentially hepatotoxic drugs were excluded.

The primary efficacy variable was survival with failure defined as death, tracheotomy or intubation at 18 months. Secondary efficacy parameters were changes from baseline in functional evaluations.

The comparison of 100 mg with placebo was defined in the protocol as the primary comparison.

In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo (survival rates were 56.8% versus 50.4% for riluzole and placebo, respectively; p value = 0.05, Wilcoxon test. p value = 0.07 log-rank test; p value = 0.002 Cox model). No interaction of the treatment effect with the type of ALS was observed.

The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day.

No changes were observed from baseline in the functional evaluation.

At the CPMP request, the Company provided a full Cox model analysis for trial 301 including all pre-defined co-variables to see if these agreed with the results of their selected model presented in the study report. The key point of interest was the level of statistical significance attached to the treatment effects in the full Cox model. As was anticipated, the P-values were less extreme (50 mg p =0.082, 100 mg p =0.003, 200mg p =0.001) but the levels of significance attached to the higher dose levels remained high.

Concerns were discussed by the CPMP on any eventual implication of the interim analysis of survival in conjunction with the early stopping of the trial. The CPMP asked the Rapporteur to contact the Chairman of the data monitoring committee of trial 301 to clarify the procedures surrounding the interim analyses. He stated that the proceedings of the data monitoring committee had been entirely confidential and had not been revealed to the Company. No Company personnel were either on the committee or present at any of the meetings of the committee. The clinical trial data provided by the Company to the committee were not decoded nor analysed by the Company. They were provided in computer readable form only, code unbroken; the code was then broken and the data analysed at the University of Reading. No recommendations were made by the data monitoring committee to the Company as a result of the interim analysis of efficacy, and no results had been communicated. The decision of the Company to conclude the trial at the end of 1994 was not related to the work of his committee, but only to the recruitment of a sufficient number of patients.

There are therefore no implications for the levels of statistical significance achieved in this trial.

Additional analysis including patients who had a strict 18 months follow-up was performed at the request of the CPMP, to eliminate any aspects of data censoring, and also to eliminate potentially reduced efficacy during the early months of treatment. In fact the results of this analysis simply mirrored those of the main analysis.

A worst case analysis for the few patients lost to follow-up was provided and was appropriately carried out. Not surprisingly, levels of statistical significance were reduced. If the reliability of the results of the Cox analysis is accepted, then robustness to their patient losses is assured.

There is clear statistical evidence in study 301 of an effect of riluzole at 100 mg on survival. The results of the analysis using the Cox model are particularly convincing (p=0.002 in original report) and are not undermined by any of the queries raised. A further analysis by the Company used more robust methods of direct stratification by risk factors in order to confirm the results of the Cox model whilst making fewer assumptions. This confirmation was successful, and similar levels of significance were achieved.

The duration of follow-up was defined in the protocol. Crossing of survival curves on prolonged follow-up is possible in theory but not objectively founded. In no way could a longer follow-up change the initial 18 months part of the survival curves, nor could it change the difference of 3 months between the two medians of survival. Eventually the curves must cross, but this does not invalidate the survival benefit established in this study.

A GCP inspection was conducted from June to September 1995 by the French Inspectorate. Four clinical centers have been audited: in Canada (Centre CA 0029), in the United States (Centre US 0711) and in France (Centers FR 0252 and FR 0255). For the French and the U.S.A. centres a joint inspection with FDA has been performed. The inspection focused on the documentation concerning the determination of the status at the end of the 18 months follow-up or at the cut-off date. Documentation of the events deaths, intubation and tracheotomy, and follow-up of patients who had discontinued investigational drug treatment was reviewed.

The compliance to treatment by patients was also reviewed.

The conclusions of the French inspectorate are the following:

" The data reviewed in the course of the inspection for the above-mentioned Clinical Centers can be considered authentic and credible, and their quality acceptable. The audit of the packaging and labelling of the drugs used in the EU sites did not identify any significant problem."

Study 302

This study was designed as a multicentre, double blind, placebo-controlled, randomised, parallel group trial and was a comparison of 100 mg with placebo in patients ineligible for trial 301, either with advanced disease or aged over 75 years or with vital capacity ratio less than 60%.

The planned size was 300 patients but only 168 patients were randomised to riluzole 100 mg/day or placebo and were followed up for 18 months: the protocolled power of the study was therefore not achieved in this study. In this population with decreased respiratory function, survival was not significantly higher in the riluzole group compared to the placebo group.

Methodologically, this was a properly conducted controlled trial. It was smaller than planned, and much smaller than study 301, but slightly larger than study 216.

There was some baseline imbalance in characteristics of patients related to prognosis but this was covered by the use of the Cox model. It therefore contributes valuable information, although the relevance of the patients included in this study to the potential target population is not entirely clear.

This study did not establish any effect of Rilutek on survival. In view of its relatively small sample size the confidence interval surrounding the finding of no difference is quite wide.

Meta analysis of studies 216, 301 and 302

A meta analysis of studies 216, 301 and 302 was carried out by the company at request of the CPMP.

©EMEA 2004

Despite the negativity of study 302, the overall statistical significance of the treatment effect is maintained (p=0.043 log-rank test). The robustness of this finding is assured by the very high overall levels of statistical significance attached to the Cox model (p=0.0004). Therefore statistically the results of study 302 could be chance findings within the context of an overall beneficial effect of Riluzole on survival.

The results of the analysis combining the three trials showed that the median survival benefit during a 18 month follow-up was approximately 2 months.

By-centre analysis

Positive results were most consistent in France, Belgium and the UK. However, small numbers makes this analysis by-centre, impossible to interpret statistically. The possible confounding with severity must also be born in mind. Statistically, the tests of interaction between the treatment effect and country were not significant, so that this pattern of result is consistent with chance.

Mortality as an end-point

If the end-point is taken as mortality only - excluding tracheotomy and intubation - the conclusions do not change. The rate of tracheotomy and/or intubation was very low in studies 216 and 301 indeed and most of these events were followed by death before reaching the cut-off date:

- study 216:
  6 tracheotomies in the placebo group: 3 deaths by the cut-off date
  5 tracheotomies in the riluzole group: 4 deaths by the cut-off date

- study 301:
  10 tracheotomies or intubation in the placebo group: 6 deaths by the cut-off date
  12 tracheotomies or intubation in the 100 mg riluzole group: 4 deaths by the cut-off date

Analysis by risk levels

An analysis separating patients in two risk levels: "high risk" and "low risk" was *a posteriori* performed, based on an initial risk index calculated for each patient. Efficacy on survival was only apparent in "high risk" patients of studies 216 and 301, thus evidencing that a benefit on survival can only be demonstrated in patients having reached a certain degree of severity of the disease.

Questions put to the company

Reservations on the clinical relevance of data observed with the treatment of ALS with Riluzole were discussed in depth by the Committee. These could be summarised as three main issues, which were put to the Company during the hearing held at the CPMP meeting on 13 February 1996:

1. Can the lack of concordance between the benefit on survival and the lack of benefit on functional scales be explained?

2. Can causes of death other than ALS influence the results of the trials?

3. Are the trials robust enough to justify the conclusions drawn from the results?

The following responses were provided:

1. Lack of correlation in ALS between survival and different functional scales:

   The Manual Muscle Scale, the Norris scales (both used in the pivotal trials) and the Appel scoring system (not used in the trials conducted with riluzole) failed - according to the published literature - to show any firm correlation with survival in ALS. This lack of correlation was also found in the studies carried out with riluzole treatment. On these grounds, the functional scales are not yet validated as surrogate markers of survival in ALS.

2. As far as the second issue was concerned, it was clearly shown that the deaths due to ALS in the clinical studies submitted were at least 95% of all deaths. This finding was expected, being the natural evolution of the disease rapidly progressive to death. Any concern about the cause of death should be allayed by the design of the randomised, double-blind, controlled trials. The baseline prognostic factors were the same in the placebo and in the Riluzole treatment arm and the overall crude mortality, in terms of time to death, (irrespective of the cause of death) was used as for the primary efficacy end-point.

©EMEA 2004

3. As far as the robustness of the clinical studies is concerned there was substantial discussion. The results obtained showed a median increase in survival time. However, because of the lack of any change in the functional scales and in symptoms the clinical relevance of this results was considered debatable and ethical considerations had to be considered.

Conclusions on efficacy at the time of granting the marketing authorisation

The original positive finding was the overall effect on the main efficacy criterion survival in study 216. This was then replicated in study 301 using the same dose of riluzole.

Study 302 conducted in patients at an advanced stage of the disease failed to establish an effect on survival. The meta-analysis of the three studies however remained positive.

The overall efficacy results appear not to vary substantially according to disease duration.

The failure to find any effect on functional end-points does not affect the reliability of the survival results but remains a concern even if a score on a specific functional scale has never been validated as a surrogate marker of survival.

There is no doubt that effects on functional end-points, if established, would help to support the survival results. If the levels of statistical significance attached to the survival effects were marginal, this might be an important point. However, the levels of statistical significance arising from the Cox model are sufficiently strong to stand on their own without the need for other support.

In all disease areas where survival data are important (e.g. AIDS, cancer) it is common practice to analyse survival data using all three statistical methods used in this application (logrank test, Wilcoxon test and Cox proportional hazard model). In general, with reasonably consistent results, an overall pattern of statistical significance in this group of tests is regarded as proof of efficacy, and statements in the protocol preferring one test over the others should not override sensible interpretation. The Cox model would be expected to achieve higher levels of statistical significance because of its greater sensitivity, and can be relied upon. The consistent outcome of the different analyses, together with the higher levels of statistical significance associated with the Cox model, is reassuring.

Post-authorisation efficacy data:

In response to a follow-up measure laid down at the time of granting the marketing authorisation for riluzole the company submitted the final study report for study 304, an efficacy study in Japanese patients with ALS. In study 304, in which 100 patients received placebo and 10 received riluzole, no significant differences were found on the primary endpoint (time to disease progression) or on tracheostomy-free survival or in a series of secondary outcome measures.

In response to a request from the CPMP, a meta-analysis of the results from patients randomised to placebo or riluzole 100 mg in studies 216, 301, 302 and 304 was submitted. In total 503 patients were randomised to receive placebo and 493 to receive riluzole.

Following evaluation of the meta-analysis, the CPMP concluded that the statistical evidence for the efficacy of riluzole is less secure. Nevertheless, given the high levels of statistical significance originally achieved in trials 216 and 301 and the overall results of the new meta-analysis, the balance of probability is still in favour of riluzole.

Clinical safety

Anaphylactoid reaction, angioedema and pancreatitis have been reported very rarely.

The following adverse reactions were reported in patients enrolled in Phase III studies conducted in North America and Europe.

The listing that follows describes all the adverse events that occurred at a frequency of 1% or more among 794 ALS patients receiving riluzole and were greater than placebo by 1%, or were serious adverse events with frequency greater than placebo during the clinical studies.

The most frequent side-effects related to riluzole were asthenia, nausea and dizziness.

Other side-effects were reported, although less commonly: abdominal pain, headache, diarrhoea, pneumonia, vertigo, and circumoral paresthesia.

Riluzole appears to have potential hepatotoxic effects with cytolytic and cholestatic effects and may cause liver dysfunction. Elevations of alanine-aminotransferase (ALT) levels to more than 3 times the upper limit of the normal range (ULN) were observed in about 10 % of the patients treated with riluzole compared to 3.7 % in the placebo group; levels increased to more than 5 times the ULN in about 3% of the patients treated with riluzole compared to 2% of the placebo treated patients. The increases in ALT usually appeared within 3 months after the start of therapy with riluzole; they were usually transient and levels returned to below 2 times the ULN after 2 to 6 months while treatment was continued. These increases were rarely associated with jaundice. In patients with increases in ALT to more than 5 times the ULN, treatment was discontinued and the levels returned to less than 2 times the ULN within 2 to 4 months.

Among approximately 5000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm^3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A third case neutropenia was associated with marked anaemia: reduction in hemoglobin levels was observed .

No adverse event on cognitive functions were observed.

No adverse effect on cardiovascular and respiratory function were observed.

There has been one significant case of overdose reported with riluzole. In an apparent suicide attempt, a patient ingested up to 30 times the recommended 100 mg daily dose. The patient developed methaemoglobinaemia that abated quickly after an infusion of methylene blue.

5.   Conclusions

Riluzole has been demonstrated to extend survival in two studies conducted in patients with ALS, but not in a third trial. Survival was the main efficacy criteria and was considered as a strong outcome measure.

The failure to find any effect on functional end-points does not affect the reliability of the survival results.

The survival data obtained with Riluzole were analysed at several time-points to explore the robustness of the findings: the general consistency of the findings is of interest, rather than specific achievements of selected significance levels. The consistent outcome of significance levels achieved in the different analyses, together with the higher levels of statistical significance associated with the Cox model, is reassuring.

An effect on functional end-points, if established, would help to support the survival results: however up to date scores on functional scales are not validated as surrogate markers of survival in ALS.

The CPMP in their meeting on 14 February 1996 adopted by scientific consensus a positive opinion on Rilutek.

The Committee in recommending the granting of a marketing authorisation felt it was important to set out in the Summary of Product Characteristics the results of the clinical trials on which the authorisation was based. The Committee felt that this was particularly important because treatment with riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of Amyotrophic Lateral Sclerosis.

The specialist physicians using riluzole will be fully aware of the data.

The therapeutic indication approved is the following:

"Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Clinical trials have demonstrated that RILUTEK extends survival for patients with ALS.

Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free.

There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS.

Safety and efficacy of riluzole has only been studied in ALS. Therefore, riluzole should not be used in any other form of motor neurone disease."

The CPMP recommended that the following information be included in the SPC under the heading "Further information on clinical trials":

"In a trial, 155 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 12 to 21 months. Survival, as defined in the second paragraph of section 4.1., was significantly extended for patients who received riluzole as compared to patients who received placebo. The median survival time was 17.7 months versus 14.9 months for riluzole and placebo, respectively.

In a dose-ranging trial, 959 patients with ALS were randomised to one of four treatment groups: riluzole 50, 100, 200 mg/day, or placebo and were followed-up for 18 months. In patients treated with riluzole 100 mg/day, survival was significantly higher compared to patients who received placebo. The effect of riluzole 50 mg/day was not statistically significant compared to placebo and the effect of 200 mg/day was essentially comparable to that of 100 mg/day. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively.

In a parallel group study designed to assess the efficacy and safety of riluzole in patients at a late stage of the disease, survival time and motor function under riluzole did not differ significantly from that of placebo. In this study the majority of patients had a vital capacity ratio less than 60%."

In October 1997, following the submission of the final report of study 304, the CPMP concluded, following evaluation of the meta-analysis, that the attempts to confirm statistically the apparent differences between trials and their results had not provided any clear answers. The statistical evidence for the efficacy of riluzole is less secure. Nevertheless, given the high levels of statistical significance originally achieved in trials 216 and 301 and the overall results of the new meta-analysis, the balance of probability is still in favour of riluzole.

The CPMP recommended that the "Further information on clinical trials" presented in the SPC be supplemented with the following statement on the findings of study 304 and the latest meta-analysis:

"In a double-blind placebo-controlled trial designed to assess the efficacy and safety of riluzole in Japanese patients, 204 patients were randomised to riluzole 100 mg/day (50 mg twice daily) or placebo and were followed-up for 18 months. In this study, the efficacy was assessed on inability to walk alone, loss of upper limb function, tracheostomy, need for artificial ventilation, gastric tube feeding or death. Tracheostomy-free survival in patients treated with riluzole did not differ significantly from placebo. However, the power of this study to detect differences between treatment groups was low. Meta-analysis including this study and those described above showed a less striking effect on survival for riluzole as compared to placebo although the differences remained statistically significant."