



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

WITHDRAWAL ASSESSMENT REPORT

FOR

Tekinex

International Nonproprietary Name:

omacetaxine mepesuccinate

Procedure No. EMEA/H/C/001244

Day 120 Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.



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LIST OF ABBREVIATIONS

| | |
|------------------|---|
| ADME | absorption, distribution, metabolism, and excretion |
| AP | Accelerated phase |
| API | active pharmaceutical ingredient |
| AUC | area under the curve |
| Bcl-2 | B-cell lymphoma |
| Bcr-Abl | Breakpoint cluster region-Abelson |
| BID | Bis in die (twice daily) |
| BP | Blast phase |
| BSA | Body surface area |
| CCyR | Complete cytogenetic response |
| CFU | Colony forming unit |
| CHR | Complete haematologic response |
| CI | Confidence interval |
| C _{max} | maximum concentration |
| CML | Chronic myeloid leukaemia |
| CML-AP | Chronic myeloid leukaemia, accelerated phase |
| CML-BP | Chronic myeloid leukaemia, blast phase |
| CML-CP | Chronic myeloid leukaemia, chronic phase |
| COSY | Correlation Spectroscopy |
| CP | Chronic phase |
| CTXOH, CTX | Cephalotaxine |
| CYP 450 | cytochrome P450 |
| DEPT | Distortionless Enhancement by Polarisation Transfer |
| DMC | Data Monitoring Committee |
| DMHHT | demethylhomoharringtonine, 4'-DMHHT |
| DSC | Differential Scanning Calorimetry |
| GC | Gas chromatography |
| GLP | good laboratory practices |
| GCP | good clinical practice |
| GUS | Glucuronidase gene |

| | |
|---------|--|
| EP | European Pharmacopoeia |
| EU | Endotoxin Unit |
| HHT | Homoharrington |
| HI | Haematologic improvement |
| HPLC | High Performance Liquid Chromatography |
| HPLC/MS | high performance liquid chromatography / mass spectrometry |
| HMBC | Heteronuclear Multiple Bond Correlation |
| HSCT | Hematopoietic stem cell transplantation |
| HSQC | Heteronuclear Single Quantum Correlation |
| HU | Hydroxyurea |
| ICH | International Conference on Harmonisation |
| ICP-OES | Inductively coupled plasma-optical emission spectrometry |
| IND | investigational new drug |
| IP | intraperitoneal |
| IPC | In-process control |
| IR | Infrared |
| ITT | Intent-to-treat |
| IV | intravenous |
| KF | Karl Fischer |
| LD(%) | lethal dose(at specified percentage) |
| LDPE | low-density polyethylene |
| LOAEL | lowest observed adverse effect level |
| MAA | marketing authorization application |
| Mcl-1 | myeloid cell lymphoma 1 |
| MCyR | Major cytogenetic response |
| MDR | multidrug resistance |
| MDS | Myelodysplastic syndrome |
| MTD | maximum tolerated dose |
| MS | Mass Spectrometry |
| NA | Not applicable |
| NCI | National Cancer Institute |
| NEL | No evidence of leukaemia |
| NLT | Not less than |

| | |
|---------|--|
| NMT | not more than |
| NMR | Nuclear Magnetic Resonance |
| No. | Number |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level |
| NYHA | New York Heart Association |
| OMA | omacetaxine |
| PCyR | Partial cytogenetic response |
| PD | Pharmacodynamic |
| Ph | Philadelphia chromosome |
| PHR | Partial haematologic response |
| PK | pharmacokinetics |
| P-gp | P-glycoprotein |
| QTc | corrected Q-T interval |
| qRT-PCR | Quantitative reverse transcription-polymerase chain reaction |
| RCP | Return to chronic phase |
| RH | Relative humidity |
| SC | Subcutaneous |
| SD | Standard deviation |
| SP | Unites States Pharmacopoeia |
| STD | severely toxic doses |
| T315I | Threonine 315 isoleucine |
| TKI | Tyrosine kinase inhibitor |
| USAN | United States adopted name |
| UV | Ultra Violet |
| WBC | White blood cell (count) |

1. RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for Tekinex (active substance omacetaxine mepesuccinate), an orphan medicinal product in the treatment of "adults with Philadelphia chromosome positive chronic myeloid leukaemia who have the Bcr-Abl T315I kinase domain mutation and who are resistant to prior imatinib therapy"

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI)

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

No information has been provided on quality of Sodium chloride 9 mg/ml solution for injection.

Origin and quality of the syringes and needles need to be documented. It should be demonstrated that the syringes and needles of the combination package fulfil the "Essential Requirements" as outlined in Annex 1 of Council Directive 93/42 EEC of 14 June 1993 concerning medical devices

The applicant is requested to provide experimental results which demonstrate the suitability of the medicinal product (drug product, solvent and medical devices) for its intended use [by lay persons].

Efficacy and safety

From the clinical point of view, there are serious problems with the submitted dossier, precluding a favourable benefit / risk assessment for omacetaxine at this time.

It is currently impossible to differentiate between potential beneficial haematological response and myelotoxicity. Additional uncertainty results from the insufficient follow up on survival and outcome of subsequent treatments. Omacetaxine is intended for self-administration by the patient or other lay-persons. Considering the significant toxicity and safety issues arising from the posology and handling (see quality part) the dossier currently fails to convince that this is a safe way to use the product.

Overall, the application is based on single arm, uncontrolled data from studies CML-202 and CML-203. While this could be acceptable if "dramatic activity" had been achieved, it is not acceptable for the actually observed modest response rates and duration of response. Without obviously outstanding benefit and in the absence of reliable historical data, comparative studies using e.g. investigator's best choice appear indispensable. During the assessment, among other problems, the following major efficacy and safety issues have been identified:

A negative benefit / risk balance - Primary endpoint for both the pivotal (CML-202) and the supportive (CML-203) study was a diffuse composite endpoint of haematological and cytogenetic response allowing for drug-induced thrombocytopenia. Baseline characteristics as presented do not allow unequivocal attribution of response to the action of omacetaxine. In addition, both currently described response rates and duration of responses are considered modest and do not outweigh toxicity and tolerability concerns.

Inappropriate posology - About 30% of all patients did not receive the proposed dosing even in the first cycle. Major deviance from planned 28 day-cycles and dosing days per cycle are still observed indicating uncertainty on how to modify dose in the light of adverse events. There is clearly a safety issue over a drug with significant toxicities which is intended for self-administration by the patient. Therefore, the recommended posology does not seem to reflect reality of the study.

Inappropriate definition of response - The definition of complete haematologic response in CML-202 and CML-203 allows for tekinox-induced thrombocytopenia and calculation of duration of response disregarded transient suppression of peripheral blood counts. A justification of the deviation from established response criteria is requested to interpret the data.

Short or lacking follow up - There is significant uncertainty of the presumed benefits due to short or lacking follow up and insufficient data maturity in CML-202 and CML-203.

Proposal for questions to be posed to additional experts

The SAG-oncology should be consulted after assessment of the Day 121 responses whether a positive benefit/risk balance for CML-CP patients could be discussed in view of the modest response rates with the risks of insufficient dose-finding and observed severe and unforeseeable safety problems. Questions will be proposed in the D150 assessment reports for adoption by the CHMP at Day 180.

Inspection issues

A GCP inspection is needed in view of a) the single pivotal trial being an uncontrolled phase II study and b) the high number of inconsistencies in the dossier with major impact on the validity of both the pivotal and the primary supportive clinical trial. A positive opinion with respect to MAA of Tekinox should not be adopted without prior GCP inspection.

The outcome of this GCP inspection and satisfactory responses to its findings should form an integral part of the responses to this LoQ.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder. It is characterised by expansion of the clone that carries the Philadelphia chromosome (Ph chromosome, Ph⁺). The Ph chromosome arises from a translocation of chromosomes 9 and 22, which results in a fusion gene that encodes the Bcr-abl protein. The Bcr-Abl oncoprotein has the properties of a constitutively active tyrosine kinase. The fusion gene confers a proliferative advantage and also an increased propensity for the clone to acquire additional genetic lesions.

CML has three phases; chronic phase (CP), which is often asymptomatic during long periods, accelerated phase (AP) and blast crisis (BP), which, especially in blast crisis, confers a shortened survival and very poor prognosis.

Treatments

Before tyrosine kinase inhibitors (TKIs), different treatments were used to treat CML, such as different chemotherapies and interferon. The only curative treatment is stem cell transplantation, however, this is associated with massive toxicity and is less frequently used after the introduction of tyrosine kinase inhibitors.

The treatment with TKIs, with imatinib as the first approved in class, significantly changed the outcome of the disease. The TKIs inhibit the constitutively active Bcr-Abl tyrosine kinase. However 20-30% of the patients are not responding to, or ultimately progresses on TKI therapy. The most common reason for resistance are point mutations in Bcr-Abl, but there are also other reasons, such as overexpression of Bcr-Abl and Bcr-Abl independent mechanisms, e.g. the regulation of drug influx/efflux.

Approximately 10-21% of patients resistant to TKI have been reported to carry the T315I mutation, corresponding to only 250 cases diagnosed every year in the EU. The replacement of the threonine with isoleucine at position 315 (T315I) in the ABL kinase domain blocks the access of the ATP-binding site by the TKI, i.e. it confers resistance to all currently authorised TKIs.

A small number of retrospective clinical studies have recently been published describing the characteristics and survival outcomes of CML patients who have the T315I mutation. In view of likely selection bias, no firm conclusion with respect to relative prognosis compared to other mutations can be drawn. However, a significantly negative effect on overall survival compared to patients with P-loop or other Bcr-Abl mutations is discussed. It was concluded that on the initial detection of the T315I mutation, patients should rapidly switch to alternative therapy. i.e. that these patients represent an area of unmet medical need.

2.2. About the product

Omacetaxine mepesuccinate (omacetaxine; also referred to as homoharringtonine or HHT) is a semisynthetic version of plant alkaloid extracted from *Cephalotaxus fortunei*, a species of evergreen that is indigenous to China. Omacetaxine is the first drug to be defined in a new class of cetaxine drugs, and has a proposed ATC code of L01XX40.

The drug product, Tekinex (omacetaxine mepesuccinate for injection, 5 mg), is supplied as a lyophilised powder that is reconstituted with 1.0 mL 0.9% isotonic saline (NaCl) immediately prior to use. The product is administered by subcutaneous injection (1.25 mg/m² twice daily for 14 (induction) or 7 (maintenance) consecutive days every 28 according to currently proposed posology). The dose will differ depending on patient's body size and might vary between 0.35 and 0.55 ml of the reconstituted product.

Tekinex may be withheld and/or the number of days of dosing adjusted for haematologic toxicities (e.g. neutropenia, thrombocytopenia) not related to underlying leukaemia. Other clinically significant non-haematologic toxicity should be treated symptomatically, and if needed, dosing should be withheld until toxicity is resolved.

The product is aimed to be prepared, reconstituted and self-administered by the patient or a caregiver at home, i.e. the concern is raised on the possible risk of under- and maybe more importantly overdosing. In the studies, a training program was used to support patient self-administration.

A similar training program to mitigate the risks associated with patient self-administration is proposed. In addition to routine risk minimisation activities, additional risk minimisation activities are included in the Risk Management Plan. A communication plan to Health care professionals (for example oncologists and visiting nurses) includes package insert, Dear Health Care Professional letter and Tekinex.com website. In addition, educational and training material for patients and nurses is included, consisting of instructional materials for training of safe practices for dosing and administration, and instructional video on self-administration by subcutaneous injection and information on proper use of accessory supplies used during the preparation and administration of the drug.

Omacetaxine is a reversible inhibitor of protein elongation and does not depend on Bcr-Abl binding for its activity. It can therefore have activity in CML independent of the mutational status of Bcr-Abl. Omacetaxine blocks peptide bond formation ultimately leading to profound, but transient inhibition of protein synthesis. A number of hypotheses on the mode of action with respect to toxicity against leukaemic cells are proposed by the applicant.

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

Omacetaxine has been under development by ChemGenex since 2001, but homoharringtonin has been tested clinically since the 1970ies in China based on activity in leukaemia from herbal medicine. The clinical development program by the applicant has focused on the treatment of patients with CML, particularly those who have failed imatinib therapy and have the T315I mutation. ChemGenex Europe SAS has obtained SME (small or median size enterprise) status with the SME number EMA/SME/038/09 in March 2009.

The current application is based on three single arm studies sponsored by ChemGenex: Study 202 in CML patients harbouring the T315I mutation (n=66; pivotal, ongoing), Study 203 in CML patients who have failed multiple tyrosine kinase inhibitors (n=65; ongoing) and Study 04.2/04.3 in patients with accelerated phase CML (n=4). In addition, the clinical database consists of a phase I pharmacokinetic study (Study 205), a retrospective collection of safety data (Study 206), a study of omacetaxine in combination with imatinib in CML patients (Study 201) and published literature data.

Scientific Advice and follow-up Scientific Advice from EMA regarding the nonclinical and clinical development program were obtained. The applicant followed the recommendations given in these Scientific Advices to a large extent with respect to non-clinical aspects.

With regard to clinical development, the general development program and a conditional marketing authorisation was discussed

With regard to CML-202 as a pivotal study, it was pointed out that there are other therapies under development for patients with T315I mutations, that subpopulations chronic and advanced (AP and BP) must be analyzed separately, and that for CP, a CyR with duration of response and possibly a CHR is a meaningful end-point while for AP and BP the meaningful endpoint is survival. Concerning safety it was not clear if the information would be sufficient to provide a risk-benefit assessment. The importance of differential toxicity against leukaemic cells compared to overall myelotoxic pharmacodynamics was stressed.

The adaptive design was discussed and it was concluded that regardless of design, a sufficient number of patients is needed. A conditional marketing approval was discussed and CHMP referred to regulation No 507/2006, Article 4(1). It was pointed out that no pre-assessment should be made but that the proposed evidence might be insufficient.

2.4. General comments on compliance with GMP, GLP, GCP

The process for the manufacturing of the finished product follows conventional pharmaceutical practices, which utilise a solution compounding step, sterile filtration, aseptic filling into vials followed by lyophilisation, stoppering of the vials, and sealing.

GMP:

The process for the manufacturing of the finished product follows conventional pharmaceutical practices, which utilise a solution compounding step, sterile filtration, aseptic filling into vials followed by lyophilisation, stoppering of the vials, and sealing. All processes performed comply with GMP requirements. GMP Inspections of the drug substance manufacturing and/or the drug product manufacturing sites and / or batch release site are not considered necessary for completion of the module 3 assessment.

GLP

All pivotal non-clinical safety studies were conducted in compliance with the Principles of Good Laboratory Practice (GLP). Many other studies referred to in the non-clinical part of the MAA are old and presented in form of literature references.

GCP

ChemGenex Europe SAS certified that all the clinical studies with TEKINEX have been conducted in accordance with GCP and the applicable national laws. A number of relevant inconsistencies and even

implausibilities have been found in the dossier. A positive opinion with respect to MAA of Tekinex should not be adopted without prior GCP inspection.

The outcome of this GCP inspection and satisfactory responses to its findings should form an integral part of the responses to this LoQ.

2.5. Type of application and other comments on the submitted dossier

This is a full Marketing Authorisation Application (MAA), via the Centralised Procedure, for a new chemical entity in accordance with Article 6 of Regulation (EC) No 726/2004, as amended, and Article 8(3)(i) of Directive 2001/83/EC, as amended.

In November 2009, the EMA decided that an accelerated procedure, as requested by ChemGenex, was not applicable.

In decision no. EMA/416511/2009, P/138/2009, dated July 15, 2009, the EMA granted omacetaxine mepesuccinate, powder for solution for injection for subcutaneous use (EMA-000484-PIP01-08) a product specific waiver for all subsets of the paediatric population and the condition: Philadelphia chromosome positive chronic myeloid leukaemia in patients who have the T315I Bcr-Abl kinase domain mutation and who are resistant to prior imatinib therapy.

While the indication CML is covered in the Draft Appendix 2 to the anticancer guideline, the molecular subset which characterised the indication creates a situation which is not addressed in the guideline. Omacetaxine is a non-selective inhibitor of protein synthesis with cytotoxic pharmacodynamics. Thus, guidance concerning the targeted TKIs with respect to endpoints is not applicable and in addition, the targeted population is very rare (estimated 250 patients in Europe per year). The population is in unmet medical need since no authorised treatment is available

Quality of the dossier

The dossier is difficult to read. In the clinical documents, a critical discussion of the study results is frequently missing.

“Pieces of the puzzle” are rather scattered over tables and appendices while the clinically relevant context of endpoints is not coherently addressed (e.g. discussion of baseline cytogenetic results was not found).

Reconstruction of the course of events for individual patients seemed to reveal inconsistencies or deficiencies with respect to the observations made during the performance of the clinical trials.

Results are presented in excessive detail (e.g. exposure by disease phase by individual cycle) that may dilute important observations. In particular, safety populations as presented in the clinical summary of safety documents rather contribute to dilute the observations made in the pivotal trial than to increase the size of the safety population.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. *Quality aspects*

Drug substance

The active substance of the drug product omacetaxine mepesuccinate or homoharringtonine (HHT) is a semi-synthetic cephalotaxine ester derived from the plant species *Cephalotaxus*.

Omacetaxine mepesuccinate (HHT) is a substance that was originally isolated from the entire plant of the evergreen tree *Cephalotaxus harringtonia* K. Koch van harringtonia present in China. It also may be manufactured through a semi-synthetic process..

The synthesis of Omacetaxine mepesuccinate is a six step process.

A comparison of semi-synthetic HHT and natural HHT was performed to study the stereochemistry and chemical structure of both compounds. These studies confirm that the stereochemistry and the chemical structure of natural HHT and semi-synthetic HHT are identical.

The possible impurities which may arise from starting materials the route of synthesis as well as degradation products have been discussed. The carryover of these impurities to the intermediates or the final drug substance has been investigated in three validation batches. The solvents used in different steps of manufacturing have discussed. The carryover of these solvents to the final drug substance has been investigated in three validation batches of the drug substance.

The specifications for the drug substance are based on batch analyses of three batches of omacetaxine mepesuccinate drug substance prepared by the commercial process, and batches used for clinical and toxicological, stability data. The methodology has been validated to meet the general requirements of the ICH guideline QB, Validation of Analytical Procedures; Methodology.

However, there are some issues identified during the evaluation of the drug specification and quality control which needs to be clarified by the applicant.

Omacetaxine mepesuccinate is packaged in a reinforced bottle closed with a silicone screw cap.

Based on the stability results provided, a proposed retest date is considered acceptable.

Drug Product

Omacetaxine mepesuccinate 5 mg/ml powder for solution for injection is manufactured. The drug product is formulated as a lyophilized powder.

Omacetaxine mepesuccinate for injection, 5 mg, will be supplied in a daily dose pack with sufficient sterile saline () solution for injection, EP, and the CE Marked syringes and needles required for reconstitution and administration by subcutaneous injection. This package will constitute a daily dose pack sufficient for two doses of Omacetaxine for injection.

No information is provided on 10 ml ampoules or vials of sodium chloride solution for injection. No studies have been presented to show the capability of the syringes to withdraw different volumes of the reconstituted product. The applicant is requested to provide studies which demonstrate the suitability of the syringe for its intended use.

The results full scale validation will be presented for three first industrial batches as soon as results are available.

Based on batch analysis data and adequacy of in process controls as well as the process simulation testing data, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces Omacetaxine mepesuccinate 5 mg/ml powder for solution for injection of consistent quality, complying with the designed specification.

The specification and control tests applied for the finished product at time of release and throughout shelf life are in compliance with general pharmacopoeial standards (Ph Eur) and ICH Guidelines (Q3B and Q6A). The specifications for release and throughout shelf life are identical except for uniformity of dosage units and the limits for related substances. The uniformity dosage units of dosage units will only be tested at release. The limits for each specification test are achievable by the production process and are supported by stability study data. The methodology for the drug product has been validated to meet the general requirements of the ICH Guideline, Q2B.

The proposed shelf-life of 3 years with "no storage precautions" is considered to be acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The control applied to the drug substance and the finished product, along with the controls over the manufacturing process of the drug substance and the drug product, support the view that the Omacetaxine mepesuccinate 5 mg/ml powder for solution for injection can be routinely manufactured to conform to the current expectations for this type of dosage form. Furthermore, the stability data submitted supports that both the active substance and the product will remain of the appropriate quality when stored as recommended storage conditions throughout the proposed re-test period and proposed shelf-life respectively. However, there are some major objections and several other concerns which have been raised during the evaluation of dossier. These issues indicate the product is not suitable for its intended use.

Conclusion on chemical, pharmaceutical and biological aspects

It cannot be denied that the quality of drug substance and drug product is only documented based on a very small number of batches. Therefore, a final conclusion can only be given when the not yet resolved quality questions will have been resolved.

3.2. *Non clinical aspects*

Pharmacology

Omacetaxine is a reversible inhibitor of protein elongation and acts by inhibiting the early steps in polypeptide chain elongation involving aminoacyl-tRNA binding and peptide bond formation. It acts independently of Bcr-Abl and is therefore not a tyrosine kinase inhibitor. The mechanism of action, particular the effect on short-lived proteins (having in mind that the drug should be given for 28 days every 14 days at the initiation phase) as well as the reversibility needs further clarification.

In vitro, omacetaxine mediates inhibition of Mcl-1, an important regulator of lymphocytic and haematopoietic stem cell survival that induces apoptosis in human leukaemic cell lines.

Omacetaxine also decreases the levels of cyclin D1 and Myc-C, proteins involved in cell cycle regulation, and has been shown to be an inhibitor of Bcr-Abl murine marrow stem cells.

The applicant has shown that omacetaxine is active against several leukaemia cell lines *in vitro* including cells lines carrying the Bcr-Abl T315I kinase domain mutation. In *in vivo* experiments (study TP20084) the applicant shows that omacetaxine is active against leukaemic cells including cells carrying the Bcr-Abl T315I gene. In this experiment the applicant also includes imatinib as a comparative drug. However, the lack of imatinib efficacy in this study is problematic since it should reduce the *in vivo* frequency of Bcr-Abl wild type cells which is not the case. In this study omacetaxine is administered orally at 0.5 mg/kg. As such the kinetic data presented in the later parts of the MAA using sc or iv administration cannot be used to address the dose needed to induce the anti-leukaemic effects observed in this study. The applicant is asked to comment on these divergences.

Antiproliferative activity of omacetaxine was tested in a broad range of human tumor cells *in vitro*. Most cell lines were considered sensitive with IC₅₀ values ranging between 20 and 80. In addition, the two main degradation products of HHT, 4'-DMHHT and CTXOH had an about 500-fold less efficacy in inducing cell cytotoxicity. The differences in cell cytotoxicity in different cell lines may be due to differences in expression of P170 glycoprotein. HHT appears to be MDR-related because MDR modifiers could restore cell sensitivity to HHT.

The *in vivo* anti-tumor activity of omacetaxine has been investigated in murine tumor models. In one mouse model of CML, treatment with omacetaxine led to a decrease of the peripheral circulating leukaemic cells and subsequently to a survival benefit. In another model, omacetaxine reduced the number of leukaemic stem cells in the bone marrow.

In studies on cardiovascular function treatment with 50 µM omacetaxine produced no statistically significant inhibition of hERG tail current in HEK293 cells when compared to the vehicle. The concentration tested (50 µM or 27.3 µg/mL) is more than 1000 times the human maximal concentration (25 ng/mL). It is therefore unlikely that omacetaxine given in lower concentration would result in significant inhibition of hERG current. Free plasma concentrations of 0.5 µM HHT would not be expected to increase QRS complex duration or QT interval.

HHT was investigated *in vitro* in combination with cytotoxic and cytostatic agents to detect potential synergistic effects. Omacetaxine in combination with cytarabine led to a significant synergistic effect. The same effects were seen with the combination of imatinib/omacetaxine and IFN-alpha/omacetaxine.

Pharmacokinetics

As shown in the conducted studies and literature data Omacetaxine is rapidly absorbed after sc administration with a T_{max} of ~0,5 h. It shows dose-dependent systemic exposure with no major sex differences. The exposure (bioavailability, IV/SC) was comparable between the two routes (AUC-SC/AUC-IV 116± 22%).

HHT has a low permeability into the cells and appeared to be subject to P-gp-mediated efflux.

The relative instability of HHT in rat plasma is due to rapid metabolism of HHT by plasma esterases; esterase inhibitors markedly improve plasma stability. Distribution in mouse and dog is comparable to that in humans. HHT is widely distributed. The highest concentration is found in the liver, kidneys and bone marrow. HHT is moderately bound to plasma protein, but binding varies across species with the lowest binding in the most sensitive species (dog) and with 40 to 50 % binding found in human plasma.

Omacetaxine is primarily metabolised in mice, dogs and human to 4'-DMHHT via plasma esterases, which is pharmacologically inactive. In human liver microsomes HHT is not subject to metabolism by the esterases. The hydrolysis (C-1' position) to cephalotaxine is minor in animals and human liver microsomes. The ability of Omacetaxine and its primary metabolite, 4'-DMHHT, to inhibit or induce cytochrome P450 isoforms was assessed in human liver tissue in order to identify the potential likelihood for drug-drug interactions. Omacetaxine is unlikely to be a CYP inhibitor or inducer at clinical relevant concentrations. 4'-DMHHT is likely to be a weak inducer of CYP3A4, but also not at the predicted clinical concentrations. Oxidative O-demethylation by hepatic CYP oxygenase is possible, although of minimal quantitative importance.

The main excretion of omacetaxine in all animal species and human is via bile and urine. No data is available of excretion in milk. Missing data on milk transfer of HHT should be adequately addressed in the SPC.

Toxicology

Omacetaxine mepesuccinate (omacetaxine; also known as homoharringtonine, HHT) has been used both as an investigational agent and for compassionate treatment in a large number of human subjects for nearly three decades. Over the years, a number of researchers have examined the toxicity of omacetaxine in several species, and these data are available in the published literature. In addition to these studies, toxicity studies sponsored by the National Cancer Institute (NCI) and ChemGenex were performed. Both acute and chronic toxicity of omacetaxine following intravenous and subcutaneous administration has been studied in mice, rats, rabbits, and dogs. Early studies, including the pilot good laboratory practices (GLP) studies, used the intravenous or intraperitoneal route. Species selection for the pivotal studies was based on species used in the IND-enabling studies sponsored by the NCI, taking into consideration metabolic and plasma protein binding differences in the different species. The mouse, a species comparable to the human in metabolism and plasma protein binding, was chosen as the rodent species, and the dog, the most sensitive species, was chosen as the non-rodent species to evaluate worst-case toxicity scenarios.

Data from ChemGenex-sponsored toxicology studies and from the literature indicated that omacetaxine is toxicologically very potent, with a high lethality in mouse, rabbit and dog and has a narrow safety margin characterized by a steep dose-response curve with very close NOAEL and STD/LD doses. Toxicity varies across species: rat is the least sensitive, dog is the most sensitive and mouse is intermediate in sensitivity (and comparable to humans in metabolism). The low tolerability in dogs is probably related to the very low plasma protein binding of omacetaxine. The higher tolerability in rats may result from the effective metabolism to the inactive metabolite 4'-DMHHT. Therefore, the rat was not considered as a relevant species to investigate toxicity of omacetaxine.

The main toxic effects in single- and repeated dose toxicity studies are consistent with the antiproliferative pharmacological activity of omacetaxine, primarily affecting lymphoid, haematopoietic, gastrointestinal and reproductive systems. In addition, cardiovascular toxicity and hepatotoxicity were observed in animal studies.

Cardiovascular effects were observed in toxicological studies in dogs and rabbits and were also the dose limiting toxicities in early IV clinical trials. Cardiovascular events seemed to be limited to the IV route as they have not been observed in toxicity studies in animals using the SC route of administration. Since cardiovascular effects were only observed after IV-administration in animal as well as clinical studies, especially after bolus IV dosing, the applicant suggests that this event is C_{max} -associated. However, a threshold level for the appearance of cardiovascular effects has not been defined by the applicant.

The exact mechanism of omacetaxine-induced cardiotoxicity has not yet been elucidated, but is probably associated with the drug's ability to affect electrical conductivity. However, since effects on the heart were also observed in mice and dogs (heart weight increase, heart epicardial fibrosis, hemorrhage) a direct cardiotoxic effect cannot be excluded. This needs to be discussed by the applicant.

The liver was identified as a target organ of omacetaxine in all animal species both after IV- and SC-administration. Hepatic effects included hepatocellular degeneration and/or necrosis in mice, dogs and rabbits and increases in hepatic enzyme activities in rats and dogs. The potential mechanism of these effects and the relevance for humans has not been discussed by the applicant.

In addition several toxic effects of unknown relation to treatment with omacetaxine have been observed in the pivotal mouse study, like myofiber degeneration of skeletal muscle, sebaceous gland atrophy, and hemorrhage in the lung. The relationship to omacetaxine treatment as well as the relevance for humans should be assessed by the applicant.

Toxicokinetic studies in mice and dogs showed that the exposure at the LOAEL and the NOAEL, respectively, was lower than the human exposure at the clinically recommended dose. Therefore, a safety margin between animal and human exposure cannot be estimated.

With omacetaxine the bacterial reverse mutation assays were negative, however an in vitro mammalian cell chromosomal aberration assay was clearly positive with and without metabolic activation. According to ICH S9 in vivo testing might not be necessary in case of positive in vitro assays for this class of product and omacetaxine has to be regarded as a potent clastogenic agent probably also in vivo, as long as data of adequate in vivo studies are not available. This should be reflected in the SPC.

Reproduction toxicity studies were performed in pregnant mice administered the drug between day 6 to 15 of gestation to investigate effects on embryo-fetal development. Omacetaxine is highly fetotoxic in mice, but not teratogenic at exposures several fold lower than the human exposure at the clinically recommended dose. Based on the mechanism of action a teratogenic effect of omacetaxine is likely. This should be discussed by the applicant.

Due to the high fetotoxic effects seen in mice the use of only one species for investigation of embryo-fetal developmental effects is acceptable.

No fertility studies were conducted, but effects on male and female reproductive organs were investigated in repeat dose toxicity studies. Omacetaxine induced changes in reproductive organs in mice, dogs and rabbits, including degeneration of the seminiferous tubular epithelium in testes (mouse), hypospermia/aspermia (mouse, rabbit, dog), ovarian cysts (mouse) and immature reproductive organs (dog). These effects have not been assessed by the applicant and a discussion on the relevance to humans has not been provided.

No peri- and postnatal toxicity studies were performed for omacetaxine which is acceptable for the treatment of patients with late stage or advanced cancer.

In studies conducted by the applicant under GLP, the active pharmaceutical ingredient (API) and the drug product used were fully characterized with respect to identity, purity, and strength.

waEcotoxicity/environmental risk assessment

The applicant has provided an environmental risk assessment phase I including calculation of a PEC surfacewater, refined and a study of the n-octanol/water partitioning coefficient according to OECD 117 (HPLC method).

The applicant has calculated F_{pen} (refined) based on the forecasted consumption of the substance in 2014. Based on the F_{pen} (refined) the applicant then calculated a PEC surfacewater, refined (0.00001µg/L) below the trigger value for a phase II environmental fate and effect analysis.

The forecast consumption is based on data on prevalence of disease. The applicant cited several references on prevalence of disease. One reference was submitted (Druker et al., 2006).

The study on n-octanol/water partitioning coefficient according to OECD 117 (HPLC method) provided by the applicant results in a log K_{ow} < 4.5 and therefore the substance is not expected to be bioaccumulative. The applicant concluded that environmental risk assessment stops in Phase I since the value of PEC surfacewater, refined is below the trigger for a Phase II assessment and furthermore the substance does not fulfil the criteria for triggering persistence, bioaccumulation and toxicity (PBT) assessment.

Discussion on non-clinical aspects

Omacetaxine has been under investigation in the United States, Europe, and China for over 20 years. An extensive bibliography of publications supporting omacetaxine's pharmacodynamics, mechanism of action, PK, metabolism and disposition and toxicology was submitted with this MAA. The applicant's nonclinical strategy primarily focused on filling in the knowledge gaps in the pharmacology, ADME and toxicology of omacetaxine by conducting new studies by considering the relevant guidelines as well as the recommendation given in the scientific advices.

Pharmacology

Omacetaxine is a reversible inhibitor of protein elongation. According to the applicant omacetaxine selectively impacted short-lived proteins, like the anti-apoptotic protein Mcl-1 and leads therefore to promotion of apoptosis. However, the selectivity of omacetaxine for short-lived proteins is questionable.

Secondary pharmacodynamic studies were not performed for omacetaxine, which is acceptable considering the long-term clinical experience with omacetaxine.

A clinical relevant toxicity is the cardiovascular toxicity of omacetaxine. Therefore, safety pharmacology studies have focused primarily on the potential for cardiovascular effects. Studies to evaluate effects on respiratory or central nervous system have not been conducted, but are not considered necessary due to the available clinical experience and the data from repeat-dose toxicity studies.

Pharmacokinetics

Absorption, distribution, metabolism and excretion of omacetaxine have been investigated in vivo in mouse, rat and dog as well as in vitro.

Species differences were observed in plasma protein binding. Plasma protein binding of omacetaxine was 2-3 % in dog, 24-32 % in mouse, 19-20 % in monkey and 40-50% in human plasma. The low plasma protein binding in dogs is consistent with the high sensitivity of this species to omacetaxine toxicity. Thus, interactions of omacetaxine with drugs that displace omacetaxine from protein binding might be clinically relevant.

Metabolism studies showed that omacetaxine is primarily metabolised to the inactive metabolite 4'-DMHHT via plasma esterases in mice, rats, dogs, and humans. In rats, rapid metabolism by esterases to 4'-DMHHT occurred indicating that the rat is not a relevant species for toxicological studies.

Toxicology

Omacetaxine is toxicologically very potent with a high lethality in animals. It has a narrow safety margin characterised by a steep dose-response curve with very close NOAEL and STD/LD doses. Many of the toxicological findings can be attributed to the antiproliferative pharmacological activity of omacetaxine, including effects on lymphoid, haematopoietic, gastrointestinal and reproductive systems. In addition, cardiotoxicity and hepatotoxicity were observed in animal studies.

Whereas omacetaxine is a clear cardiovascular toxic agent, there are some hints that it also induces direct cardiotoxic effects. This should be discussed by the applicant. In addition, a threshold level should be defined for the appearance of cardiovascular effects.

Effects in the liver (hepatocellular degeneration/necrosis, increase in hepatic enzyme activity) have been observed in all animal species. The relevance of these effects for humans and the potential mechanism has to be discussed by the applicant.

In addition, for several other toxic effects observed in the pivotal mouse study, like myofiber degeneration of skeletal muscle, sebaceous gland atrophy, haemorrhage in the lung, the relationship to omacetaxine is not clear.

No carcinogenic studies have been performed for omacetaxine. However, on the basis of the in vitro tests on genetic toxicology omacetaxine has to be regarded as potentially clastogenic in vivo also and a relevant carcinogenic potential can not be excluded. This should be mentioned in the SPC.

Omacetaxine is highly fetotoxic in mice when administered during embryo-fetal development. Teratogenic effects were not observed in mice, but are likely due to the mechanism of action. This point should be addressed by the applicant and a rewording of the SPC may be needed. Specific fertility studies have not been conducted. In repeated dose toxicity studies effects on male and female reproductive organs were observed. An assessment of these effects and a discussion on the relevance for humans should be provided by the applicant.

Due to the high fetotoxic potential of omacetaxine, reproduction toxicity studies in a further species are not regarded necessary. Also, the lack of pre-postnatal developmental studies is acceptable considering the indication intended for omacetaxine in patients with late stage or advanced cancer.

Ecotoxicity/environmental risk assessment

The applicant has provided an environmental risk assessment phase I including calculation of a PEC_{surfacewater, refined} and a study of the n-octanol/water partitioning coefficient according to OECD 117 (HPLC method).

The applicant has calculated F_{pen} (refined) based on the forecasted consumption of the substance in 2014. Based on the F_{pen} (refined) the applicant then calculated a PEC_{surfacewater, refined} (0.00001 µg/L) below the trigger value for a phase II environmental fate and effect analysis.

The forecast consumption is based on data on prevalence of disease. The applicant cited several references on prevalence of disease, but only one reference was submitted (Druker et al., 2006).

An F_{pen} refinement in phase I of environmental risk assessment is only acceptable based on the submission of published data on prevalence of the disease. This criterion is not sufficiently fulfilled.

But in the case of Tekinex, the CHMP abstains from further requests on prevalence data since based on the orphan designation document by the EMA (EU/3/04/224) a prevalence of the disease of 0.9 in 10,000 people is documented. Based on this prevalence and a maximum daily dose of 5mg the calculation of PEC_{surfacewater, refined} results in a value of 0.00022µg/L. This value is below the trigger for a Phase II assessment.

The study on n-octanol/water partitioning coefficient according to OECD 117 (HPLC method) provided by the applicant is valid and plausible. The resulting log Kow is < 4.5 and therefore the substance is not expected to be bioaccumulative. Furthermore the substance does not fulfil the criteria for triggering persistence, bioaccumulation and toxicity (PBT) assessment.

Therefore finally the CHMP agrees with applicant and it is assumed that the medicinal product Tekinex is unlikely to represent a risk for the environment following its prescribed usage in patients.

Conclusion on non-clinical aspects

Overall, the primary pharmacodynamic studies showed that omacetaxine exerts its antitumor activity via inhibition of protein elongation. However, selectivity to short-lived proteins has not been demonstrated in these studies. General toxicity studies mainly focused on the cardiovascular effects of omacetaxine.

From the pharmacokinetic point of view, the mice, a species comparable to the human in metabolism and plasma protein binding, was the most relevant rodent species for non-clinical efficacy and safety studies. The dog was considered the most sensitive species for safety studies due to the low plasma protein binding.

Overall, the toxicological programme revealed that omacetaxine is toxicologically very potent, with a high lethality in animals. Toxicological effects are mainly attributed to antiproliferative pharmacological activity, but effects independent of the pharmacological activity are also possible, like hepatotoxicity and cardiotoxicity. Omacetaxine has to be regarded as a potent clastogenic agent and a relevant carcinogenic effect cannot be excluded. Reproduction toxicity studies showed that omacetaxine is highly fetotoxic. Based on the mechanism of action a teratogenic effect is likely. Since many of these toxic effects are still under discussion, specific comments on the SPC are regarded premature.

An environmental risk assessment Phase I including calculation of a PEC_{surfacewater, refined} and a study of the n-octanol/water partitioning coefficient according to OECD 117 (HPLC method) is provided. The CHMP agrees with applicant and it is assumed that the medicinal product Tekinex is unlikely to represent a risk for the environment following its prescribed usage in patients.

3.3. Clinical aspects

The early clinical development of homoharringtonine (HHT) began in China based on indications of activity in leukaemia from Chinese herbal medicine formulations in the early 70ies. A formulation based on a plant extract is commercially available in China for the treatment of haematologic malignancies. ChemGenex developed a subcutaneous dosage of a semisynthetic form of HHT, called omacetaxine intended for self-administration by patients in an out-patient setting.

– **Tabular overview of clinical studies**

Table 1: Clinical trials performed with omacetaxine

| Study Identifier | Patient Population | Phase / Design | No. of Subjects total and per phase of disease | Study posology | Primary endpoint | Notes |
|---|---|--|---|---|--|--|
| Pivotal Study CML-202 (2006 - ongoing) EudraCT Number: 2006-000176-32 | CML patients with T315I mutation and prior failure with imatinib | Phase II Uncontrolled, Open-Label International Multicenter (n=32) | 66 CML-CP: 40 CML-AP: 16 CML-BP: 10 | Planned: Induction: SC omacetaxine 1.25 mg/m ² twice daily for 14 consecutive days every 28 (±3) days (up to 6x) Maintenance: SC omacetaxine 1.25 mg/m ² twice daily for 7 consecutive days every 28 (±3) days up to 24 mo As performed: no distinction of induction or maintenance treatment | Clinical response (centrally adjudicated) Composite endpoint depending on phase of disease: CP: CHR or MCyR of ≥8 w duration AP/BP: CHR, NEL, RCP or MCyR of ≥4 w duration | – Patients in ongoing CHR were eligible – Definition of CHR allows for drug-induced thrombocytopenia and, with respect to duration of response for suppression of PBC – Insufficient follow-up after discontinuation of study with respect to survival, type and outcome of subsequent treatment |
| CML-203 (ongoing) (relevant supportive) EudraCT Number: 2007-001286-15 | CML patients with multi TKI failure/intolerance | Phase II Uncontrolled, Open-Label International Multicenter (n=28) | 65 CML-CP: 30 CML-AP: 20 CML-BP: 15 | see CML 202 | see CML-202 | Immature data |
| 04.2/04.3 (Completed) EudraCT Number 2006-000176-32 | CML-AP patients | Phase II multicentre, single-arm, open-label | CML-AP: 4 | regimen as CML-202, but only 1-2 induction cycles, maintenance until disease progression | Number of patients who achieved a haematological response (CHR or RCP) | Sample size critically low |
| CGX-635-205 (Completed) | PK study in patients with relapsed or refractory haematologic malignancies and solid tumors without bone marrow involvement | Phase I open-label, non-randomized, multicenter (n=3) | 21 Patients with solid or hematologic tumours | induction treatment of pivotal | PK Safety (QT) | |

| | | | | | | |
|---|---|-----------------------------|----|--|--|---|
| CML-201 (Completed) Registration number not found | CML- CP(refractory or resistant to imatinib); AP, BP (newly diagnosed or previously treated with imatinib) | Phase II Open-Label | 15 | IV omacetaxine 2.5 mg/m ² /d x 5 days every 4 weeks; Imatinib – 400 mg daily PO for CP; 600 mg daily PO for AP and BP | Hematologic, cytogenetic, and molecular responses and the duration of these responses. | Meaningful response was defined as follows: (a) CML- CP patients: patients who were not in CHR at the start of the study must have achieved at least a CHR, and patients who were in CHR at start of the study must have demonstrated an improvement in their cytogenetics; (b) CML-AP and -BP patients: Patients must have converted to at least CML-CP |
| CML-206 (ongoing) Registration Number not found | Retrospective evaluation of safety in CML and AML patients receiving compassionate use in France (ATU) | Retrospective evaluation | 76 | IV, SC, monotherapy or in combination | Safety | Too heterogeneous with respect to dosing regimen |
| AML-204 (ongoing) EudraCT Number: 2006- 004517-17 | Relapsed or refractory AML patients | Phase II Open-Label | 13 | Induction: SC omacetaxine 2.5 mg/m ² twice daily for 9 consecutive days every 28 (±3) days Maintenance: SC omacetaxine 1.25 mg/m ² twice daily for 7 days every 28 (±3) days | | |
| MDS-201 (Completed) Registration number not found | IV MDS Study | Phase II Open-Label | 9 | Omacetaxine 2.5 mg/m ² IV daily x 7 days every 4 weeks. Dose increased to 3.0 mg/m ² if no response after the first course Maintenance: omacetaxine 2.5 mg/m ² IV daily x 7 days every 4 weeks for a total of 12 courses | Complete remission, partial remission (PR) or hematologic improvement (HI). | |

Pharmacokinetics

The pharmacokinetic data for Tekinex includes *in vitro* studies using human materials, one key Phase I pharmacokinetic study (Study 205) conducted by ChemGenex and published literature describing three

previously conducted clinical studies with pharmacokinetics as one of the objectives. Data from two studies (the ChemGenex study 205 and Levy *et al*, 2006) were conducted using the subcutaneous route of administration while the two other studies (Savaraj *et al*, 1986, Savaraj *et al*, 1987) used intravenous administration.

The Applicant states that the drug substance and drug product used in the pivotal clinical studies sponsored by ChemGenex are identical to those proposed for commercial use. However, in the pivotal phase II clinical study no. 202, batches manufactured at another manufacturing site were used in addition to batches manufactured at the main site.

The absolute bioavailability at SC administration is not known. Results from Study 205 indicated that omacetaxine was rapidly absorbed after subcutaneous injection of a dose of 1.25 mg/m², with measurable omacetaxine plasma concentrations at 0.5 hours after injection (first sampling point). Median concentrations were higher on Day 11 than on Day 1 indicating some accumulation upon twice daily administration, which is not unexpected based on the reported half-life. The inter-patient variability was moderate to high, with CV% ranging from 30% to 75% in key pharmacokinetic parameters. Intra-individual variability has not been addressed by the Applicant.

Published PK data following *intravenous* administration indicate that omacetaxine has an initial volume of distribution of 0.6 L/kg and a steady state volume of distribution of 1.8 L/kg suggesting wide tissue distribution.

Two different methods for evaluating protein binding were used, ultracentrifugation indicated 40-50% binding in human plasma, while equilibrium dialysis indicated binding >12%. The discrepancy might possibly be due to different degradation of omacetaxine in plasma. Nevertheless, plasma protein binding of omacetaxine appears not to be important.

Data suggests that omacetaxine and its major metabolite have relatively low permeability over cell membranes. They also appear to be substrates to Pgp and/or other efflux transport proteins that are inhibited by Cyclosporin A.

Omacetaxine is a cephalotaxine ester and previous literature data has suggested that the primary metabolite of omacetaxine is the demethylated homoharringtonine acid product (HHT-acid; 4'-DMHHT), which has been shown to be pharmacologically inactive. It is suggested to be formed by ester hydrolysis via plasma esterases and microsomal esterases. Another, minor, metabolite is cephalotaxine, also formed via hydrolysis and pharmacologically inactive.

In vitro studies showed that omacetaxine was hydrolysed in human plasma, but that in human liver microsomes, CYP-mediated metabolism as well as ester hydrolysis was very low.

Omacetaxine plasma concentrations displayed bi-exponential decay. The half-life after subcutaneous administration averaged about 7 hours on both Days 1 and 11. In another study with intravenous administration, the mean terminal half-life was 9.3 hours. The half-life of the suggested primary metabolite, 4'-DMHHT, was more than twice that of omacetaxine and might have been underestimated due to a short sampling time. The AUCTAU of the metabolite was approximately 13% of the omacetaxine AUCTAU. Cephalotaxine was only detected at very low levels in plasma. It is unknown whether there are other metabolites circulating in plasma.

Based on a published study with ³H-labelled omacetaxine administered intravenously, less than 30% of a dose is excreted in urine and, thus, about 70% of a dose would be expected to be excreted in faeces. About 38% of the material in urine (10% of the dose) was unchanged omacetaxine, and a similar amount was accounted for by one major metabolite in urine, uncharacterised in this study but which could possibly be the hydrolysis product 4'-DMHHT. It is, however, unknown whether drug-related material in faeces, i.e. the major part of a dose, is excreted mainly as unchanged omacetaxine, as 4'-

DMHHT or as other, unidentified metabolites. Thus, the main elimination pathway for omacetaxine is unknown. It could be biliary excretion of unchanged drug, plasma hydrolysis to 4'-DMHHT, or one or several unknown metabolism pathways. Renal excretion of unchanged drug appears to be a minor pathway.

Special populations

There are no studies in special populations.

Renal excretion of unchanged omacetaxine is likely a minor elimination pathway, and the general warnings suggested by the Applicant for the SPC concerning renal impairment are considered sufficient.

Hepatic impairment is not expected to largely affect the hydrolysis of omacetaxine to 4'-DMHHT. However, if biliary excretion is the primary elimination mechanism for omacetaxine, hepatic impairment may be a risk factor leading to higher plasma exposure. Moreover, although CYP metabolism is expected to be minor there might be unidentified metabolism pathways for which hepatic function is important. Due to the toxic nature of the compound and the target population, a specific study in hepatic impairment might not be feasible. A contra-indication merely due to lack of data is not considered adequate, and the Applicant should therefore carefully discuss how patients with hepatic impairment should be monitored in clinical practise.

There is no information on the impact of weight or body surface area (BSA) on the pharmacokinetics of omacetaxine. The Applicant suggests dosing based on BSA. However, if clearance is not related to body size, dosing by body size might possibly lead to underexposure in small patients and overexposure in obese patients. The Applicant should discuss especially the risk for overdosing in patients with large BSA, and whether a maximum (flat) dose should be recommended above a certain bodyweight or BSA.

Omacetaxine is not indicated in children and a PIP waiver has been granted. The warning in the SPC regarding use in children and adolescents should be stronger than currently proposed by the Applicant.

Interactions

Since biliary excretion might be an important route of elimination for omacetaxine, the substance might be susceptible for interactions on a transport protein level. Omacetaxine has been suggested to be a substrate to Pgp but might very well be a substrate for several hepatobiliary transporters, and the potential interaction risk needs to be described in the SPC. It should also be evaluated in vitro whether omacetaxine is an inhibitor of important biliary transporters.

Based on currently available data, the risk for effects of other substances on omacetaxine at a metabolic level might be considered low, but since the elimination of omacetaxine has not been fully characterised, there might be unidentified metabolism pathways that could be affected by concomitant medications. This needs to be reflected in the SPC.

Concerning effects of omacetaxine on other substances on a metabolic level, based on in vitro data a risk for interactions involving time-dependent inhibition of CYP3A4 by omacetaxine or induction of CYP3A4 by the primary metabolite cannot be excluded.

Due to the toxic nature of the compound and the target population, it is acknowledged that clinical interaction studies might not be feasible. Thus, the SPC would need to contain adequate warnings regarding the uncertainties and potential interaction risks.

Pharmacodynamics

Tekinex is considered to be an other antineoplastic agents according to pharmacotherapeutic group with ATC of L01XX40. From the mode of action Omacetaxine seems to be a first in class product.

As the agent is highly toxic in particular, haematotoxic clinical evaluation of PK/PD data has to be restricted to patients. Investigations in healthy volunteers are unethical.

Pharmacodynamic was thus mainly investigated in non-clinical models with regard to effects on haematopoiesis in blood malignancies and cardiac toxicity. As the product is additionally applied for the treatment of T315I mutant CML, a subpopulation of orphan disease CML, the overall clinical study program is limited. In the application there are no studies on dose/plasma concentrations and effect, furthermore there are no markers for response evaluated. No information on pharmacodynamic aspects of Omacetaxine is given in the clinical overview respectively in the Summary on clinical Pharmacology document.

Omacetaxine acts as a reversible inhibitor of protein elongation. Proteins that are presumably affected are short-lived proteins such as transcriptional factors. Other examples are Mcl-1, a protein that is a regulator of lymphocytic and haematopoietic stem cell survival, but also proteins involved in cell cycle regulation such as cyclin D1 and Myc-C.

Unlike TKIs, omacetaxine is independent of Bcr-Abl binding for activity and consequently is independent of mutational status of Bcr-Abl. The effect of omacetaxine is hence not particular in patients with T315I mutations but rather a general effect in lymphocytic and haematopoietic cells.

In study CGX-635-205, single and multiple dose pharmacokinetics, safety profile, anti-tumour effect and QT of omacetaxine subcutaneously was evaluated.

Twenty-one patients were included, the vast majority with solid tumours. Omacetaxine was dosed 1.25 mg/m² BID in 14 days in a 28 day cycle.

Only seven patients continued to have an efficacy evaluation at end of cycle 2, of those three had stable disease, the others progressive disease. With regards to safety all patients had AEs and Grade 3-4 AEs, five patients had SAEs and one patient died from an AE. The most common AEs were haematologic gastrointestinal and fatigue. A QT analysis showed that no patient had >60 msec increase in QTc. The highest mean changes was about 5 msec compared to predose and recorded at 8 hours. Two patients as assessed by Bazett's correction method and one patient by Fridericia's correction method had an increase above 470 msec. There was no correlation to peak plasma concentrations.

The applicant has not performed studies on pharmacodynamics and overall it seems that many aspects with regard to this item are unknown at present. However, secondary pharmacology studies did not find evidence for cardiac toxicity resulting from disruption electrical conductivity. Data for hyperglycaemia observed might have identified insulin resistance due to Omacetaxine treatment as the cause of this disorder. Genetic differences as well as drug-drug interactions with regard to pharmacodynamic have not been reported. The PK/PD relationship was not discussed in the submitted documents and seems to be uncertain, in particular in the applied target population.

The drug has been under development for more than 30 years and literature is available on the mode of action. The toxicology profile of the agent is documented and has been confirmed in human since early clinical pilot studies in the 1980ies. Cardiac toxicity was assessed as manageable after the switch from the intravenous to the subcutaneous form of administration. The product is applied for the use in a highly selected population of T315I CML patients, whose treatment options and prognosis are similar to the situation in CML patients prior to the introduction of TKIs. In summary, risks resulting from the still incomplete knowledge on Omacetaxine' pharmacodynamic seem acceptable for the proposed indication.

Conclusions on clinical pharmacology

Some findings, in particular regarding the metabolism and elimination or excretion of Omacetaxine, remain uncertain. This is not an unusual finding for an antiproliferative agent with high cytotoxicity. The clinical data is very limited, no data is submitted regarding plasma concentration and effect or safety. The safety profile is consistent with a general effect on shortlived proteins like transcription factors, cell-cycle regulators and lymphocytic haematopoietic stem cell survival. A limited QT analysis in 21 patients did not show any major effect on QT.

The pharmacokinetic data is not sufficient to draw conclusions on the major elimination mechanism for omacetaxine, and thereby effects of e.g. organ impairment or concomitant treatment with potentially interacting drugs cannot be predicted. Due to the toxic nature of the substance, clinical studies in special populations or drug-drug interaction studies may not be feasible, and the potential risks will therefore largely need to be handled by warnings in the SPC.

Clinical efficacy

Dose-response studies

The applicant cites two published studies as dose-finding studies for omacetaxine SC, one in acute myeloid leukaemia (AML) (Levy 2006), one in CML patients (Quintas-Carmada et al. 2007). The dose escalation study in AML showed a MTD at 5mg/m² for 9 days.

The authors of these studies also referred to data published earlier using homoharringtonin (HHT) IV (O'Brien 1995). Doses for omacetaxine administered SC were not further escalated compared to homoharringtonin administered IV. The dose for the pivotal trial of 1.25 mg/m²/day SC administered twice daily d1-14 every 28 days, followed by 7 dosing days as maintenance was only described in less than 10 patients. One PK study was performed by the applicant only after the pivotal trial had been initiated. No further studies were discussed by the applicant.

Main clinical studies

The pivotal study submitted for the MAA is the trial CML-202, the only trial performed in the molecularly selected population relevant for the applied indication. A supportive trial is CML-203, which is identical with respect to trial design but includes a broader patient population (see supportive study). In addition, the applicant refers to further reports summarising clinical experience in CML, AML or MDS (see table above).

CML-202 A Phase II Open-Label Study of the Subcutaneous Administration of Homoharringtonine (Omacetaxine) (CGX-635) in the Treatment of Patients with Chronic Myeloid Leukaemia (CML) with the T315I Bcr-Abl Gene Mutation (PIVOTAL trial)

EudraCT Number: 2006-000176-32

First patient in: September 20, 2006

Status: Ongoing, data cut off was March 6, 2009

Design: Study CML-202 is an ongoing (date of data cut-off for this analysis is March 6, 2009) multi-center ($n \geq 24$; needs clarification), single-arm, open-label study performed in the United States, France, Germany, Canada, United Kingdom, Poland, Hungary, India and Singapore.

In- and exclusion: Inclusion was determined by the presence of the T315I mutation of the BCR-Abl fusion protein in addition to prior failure of imatinib treatment (according to accepted criteria). In view of the unresponsiveness of this mutation to any known TKI, all phases of CML were eligible. For AP and BP patients, prior imatinib had to have been escalated to at least 600 mg, while no dose escalation was required for CP patients.

Loss of CHR or CyR to prior treatment were required, but patients in ongoing complete haematologic response were eligible. Preceding or concurrent treatment with hydroxyurea, leukapheresis or anagrelide for symptomatic control was permitted as was on-study treatment with hydroxyurea in patient with rapidly progressive disease. Patients eligible for stem cell transplantation were excluded as well as patients with cardiac disease. No minimal life-expectancy was required.

Treatment: It was initially planned to give patients first induction therapy (SC omacetaxine 1.25 mg/m² twice daily for 14 consecutive days every 28 (\pm 3) days) followed by maintenance therapy (SC omacetaxine 1.25 mg/m² twice daily for 7 days every 28 (\pm 3) days) upon response to tekinox for patients in chronic phase. Responding CML-AP and CML-BP patients were to continue to receive additional cycles of induction therapy or may have converted to maintenance therapy, as determined by the patient's clinical status and at the discretion of the principal investigator.

Upon performance of the trial, treatment was no longer distinguished according to induction and maintenance therapy with physicians aiming at maintaining a 28-day omacetaxine treatment cycle in order to optimise efficacy and maximise tolerance. Continuation of therapy beyond 24 months was determined by the sponsor and the principal investigator, based on the response status of the patient and the safety data available at the time.

Compliance: Omacetaxine has been developed for self-administration by the patient. Patients were provided with a diary (used as source documentation) in which to record their omacetaxine injections. If the patient diary was missing or indicated that a dose administration was unknown and dosing records existed for previous cycles, the missing dose was imputed using the last known doses not to exceed the number of doses administered in the previous cycle.

Primary endpoint is the percentage of patients achieving DMC adjudicated composite endpoint of "clinical response" defined differently as per disease phase. The primary endpoint allowed for concomitant drug-related thrombocytopenia. Minimal requirements for achieving clinical response is complete haematologic response (CHR) for CP-CML, while for AP/BP-CML, No-evidence-of-Leukaemia (NEL) or Return-to-CP (RCP) are sufficient. Major cytogenetic response (complete or partial) is included into the composite endpoint for all disease phases. In contrast to the complete haematologic response

definition, NEL or RCP do not need confirmation after a pre-specified time interval (8 weeks for CML-CP and 4 weeks for CML-AP or CML-BP).

Secondary endpoints include time to and duration of response (haematologic or cytogenetic), molecular response, progression-free and overall survival. Treatment-related suppression of peripheral blood counts (PBC) due to continuing maintenance course with omacetaxine therapy will not impact on the requirement for normal peripheral blood counts and ANC in calculation of the duration of CHR, if it is clear that the PBC suppression is temporally due to the prior omacetaxine maintenance treatment course, e.g., occurring at the expected time for nadir blood counts following a treatment cycle of omacetaxine, and the PBC suppression is transient.

Study population: A total of 66 patients (40 CML-CP, 16 CML-AP, and 10 CML-BP) were included in the ITT. Subgroup analyses by haematologic response status and hydroxyurea use at baseline (defined as within 48 hours of baseline laboratory assessments) were also reported. The majority of the overall study patients (n= 42, 63.6%) had discontinued from the study at the time of data cut off. Ongoing patients predominantly were in chronic phase (n=22 of overall n=24). Disease progression was the most common reason for discontinuation, both in the individual phases and overall.

Baseline demographics: Over all disease phases, there were 46 males (70.0%) and 20 females (30.0%) with a median age of 58 years (range, 19 to 83 years) enrolled in the study. The majority of patients were Caucasian (53; 80.3%). The vast majority of patients had adequate cardiac function with NYHA class I (92,4%) or II (7,6%) without clinically relevant findings in the baseline ECG results. Only few patients in AP and BP had a performance status above 2 (overall ECOG 0 (53%); 1 (40,9%); 2 (4,5%), 1 (1,5%)). Patients in BP-CML are substantially younger compared to patients of the other disease phases (median 50 years compared to median age of 59 years(CML-CP) patients or 62 years (CML-AP) patients).

CML disease characteristics and haematologic status at baseline: All patients had confirmation of the Bcr-Abl T315I mutation, but only 65.2% confirmed by a reference laboratory. In total, 23 patients had evidence of clonal evolution at baseline, including 10 out of 40 (25.0%) CML-CP patients, six out of 16 (37.5%) CML-AP patients, and seven out of 10 (70.0%) CML-BP patients. Some patients were reported being in CHR upon enrolment (n=8). The median time from initial CML diagnosis was 48.9, 90.5 and 35.7 months in chronic, accelerated and blast phase respectively.

All patients had T315I mutations by local laboratories. However only 43 (62.5%) of the patients had their mutation status confirmed by central reference laboratory, for the remaining the sample was testing negative (10), not collected (6), poor quality (5), lost or broken (2).

Treatment history: All patients had received prior treatment with imatinib and 70% of them received at least one additional TKI. Treatment with dasatinib was more common than treatment with nilotinib for every disease phase. Most of the patients stopped prior treatment less than 3 months before enrolment for all disease phases and overall (63,6%). Imatinib dose had been escalated to 600-800 mg in the majority of included patients. Best response to imatinib treatment was CHR in 53% of patients and MCyR in 24% of patients. Compared to initial treatment with imatinib, rates of a MCyR almost halves for TKI treatment other than imatinib, a frequent phenomenon with subsequent therapies. Patients in advanced phases of disease (AP/BP) were more frequently previously treated with highly cytotoxic substances using anthracyclins or alkylating agents compared to patients in CP. Overall 39 patients (n=59%) were receiving or had recently received hydroxyurea (CML-CP n=23; CML-AP n=11;CML-BP n= 5), without achieving CHR however in spite of seemingly adequate dosing of hydroxyurea (n=36).

Primary efficacy analysis: The primary analysis of categorical classification of the best haematologic and cytogenetic response by disease phase, assessed by the independent DMC as reported by the applicant is presented in the table below:

Table 2 Best Haematologic and cytogenetic response by disease phase DMC classification (ITT)

| Category/Statistic | Cohorts | | | Total (N = 66) |
|---|---------------------|-------------------------|-------------------|-------------------|
| | Chronic (N = 40) | Accelerated (N = 16) | Blast (N = 10) | |
| Overall hematologic response ^a | 34 (85.0%) | 6 (37.5%) | 3 (30.0%) | 43 (65.2%) |
| One-sided 95% lower confidence limit | 70.16% | 15.20% | 6.67% | 52.42% |
| Hematologic response categories | | | | |
| CHR | 34 (85.0%) | 5 (31.3%) | 2 (20.0%) | 41 (62.1%) |
| PHR | 0 | 0 | 0 | 0 |
| HI | 0 | 2 (12.5%) | 1 (10.0%) | 3 (4.5%) |
| RCP | NA | 1 (6.3%) | 1 (10.0%) | 2 (3.0%) |
| NEL | NA | 0 | 0 | 0 |
| No response | 6 (15.0%) | 8 (50.0%) | 4 (40.0%) | 18 (27.3%) |
| Unevaluable | 0 | 0 | 2 (20.0%) | 2 (3.0%) |
| Overall (any) CyR | 11 (27.5%) | 1 (6.3%) | 0 | 12 (18.2%) |
| MCyR ^a | 6 (15.0%) | 1 (6.3%) | 0 | 7 (10.6%) |
| One-sided 95% lower confidence limit | 5.71% | 0.16% | 0 | 4.37% |
| CyR categories | | | | |
| CCyR: 0% Ph+ cells ^b | 4 (10.0%) | 1 (6.3%) | 0 | 5 (7.6%) |
| PCyR: > 0 - 35% Ph+ cells ^b | 2 (5.0%) | 0 | 0 | 2 (3.0%) |
| Minor: > 35 - 65% Ph+ cells | 0 | 0 | 0 | 0 |
| Minimal: > 65 - 95% Ph+ cells | 5 (12.5%) | 0 | 0 | 5 (7.6%) |
| No Response: > 95% Ph+ cells | 23 (57.5%) | 15 (93.8%) | 8 (80.0%) | 46 (69.7%) |
| Unevaluable | 6 (15.0%) | 0 | 2 (20.0%) | 8 (12.1%) |

^a Overall hematologic response included confirmed CHR for CML-CP patients, and included confirmed CHR, NEL or RCP for CML-AP and CML-BP patients; MCyR included CCyR or PCyR.

^b Included both confirmed and unconfirmed response. Unconfirmed response was based on a single bone marrow cytogenetic evaluation where a confirmatory evaluation was not available.

Abbreviations: NA = not applicable; PHR = partial hematologic response.

All patients in chronic phase with CHR at baseline maintained a CHR and in one patient CHR deepened into a major cytogenetic response. The majority of the responses were seen early. The majority of the haematologic responses occurred in cycle 1 and the cytogenetic responses in cycle 2-3. In the patients in chronic phase with MCyR, four achieved a CCyR (all confirmed and ongoing) and two achieved a PCyR (one transient, one confirmed and ongoing). The MCyR in the one patient with accelerated phase was ongoing. Hydroxyurea was used for symptomatic treatment prior to study entry and was allowed

for patients with rapidly progressive disease on study. CHR rate was lower in patients with prior or concomitant HU treatment compared to patients who either did not use HU prior to the study or discontinued HU at baseline. No patient in accelerated or blast phase was in CHR at baseline.

Secondary efficacy analysis

Haematologic response was achieved in the majority of patients during the first treatment cycle and in within 8 days for 25% of patients. All responses were achieved within 3 treatment cycles regardless of disease phase. For duration of response and cumulative dose, a high standard deviation and range for mean and median, respectively are observed.

Five of 40 patients in CP died between study day 31 and 143 and within 7-42 days after the last dose of study drug. Two patients only received 1 cycle or 3 cycles, respectively and one patient received 5 cycles and all but one were classified as non-responders. Follow-up for survival ended with study discontinuation resulting in a high rate of early censoring.

Table 3 CML-202 Secondary efficacy endpoints per disease phase

| | Chronic (n=40) | Accelerated (n=16) | Blast (n=10) |
|---|-----------------------------|-------------------------------|---------------------------|
| Molecular response | | | |
| N (evaluable) | 30 | 11 | 4 |
| Number of molecular responses (depending on housekeeping gene used) | 2-6 | 1-2 | 0 |
| Duration of overall haematologic response (months) | | | |
| N | 34 | 6 | 3 |
| mean (SD) | 8.8 (6) | 6 (5) | 2.6 (1.7) |
| median (range) | 7.7 (1.7 – 23.6) | 3.9 (1.7 – 14.8) | 2.2 (1.2 -4.4) |
| Duration of major cytogenetic response (months) | | | |
| N | 6* | 1 [§] | 0 |
| mean (SD) | 6.6 (5.3) | 1.9 | NA |
| median (range) | 6 (0.8 – 16.1) | 1.9 (1.9-1.9) | NA |
| Overall survival | | | |
| N | 40 | 16 | 10 |
| deaths on study | 5 ^{&} | 4 | 7 |
| median OS (months) | NA | 18.8 | 1.8 |
| Progression[‡]-free survival | | | |
| Median (95% CI) months | 11.2 (95% CI: 6.6, 14.7) | 3.1 (95%CI 1.8, 4.3) | 1.2 (95% CI: 0.7, 2.4) |

* one transient, 5 ongoing at data cut-off § ongoing at data cut-off ‡ definition currently unclear
& n=4 non-responder, n=1 responder

Clinical studies in special populations

None performed. Subgroup analysis based on age or gender revealed no notable difference.

Analysis performed across trials (pooled analyses AND meta-analysis)

None performed.

Supportive studies

The most important supportive trial in CML-203 which was performed following the same protocol as the pivotal trial (see below).

Studies 04.2/04.3

Single arm studies evaluating omacetaxine in accelerated phase CML, 04.2 was an induction phase study including four patients, 04.3 was a maintenance study where the two patients who achieved a response were included. The responses were NEL and CHR. The patients were discontinued after three and ten cycles respectively due to thrombocytopenia and persistent pancytopenia respectively.

Other studies

Retrospective safety data from 76 patients are included in study report CML-206, in addition safety data is provided from fifteen patients with CML who are treated with omacetaxine in combination with imatinib. Further data is provided from 13 AML patients in study AML-204 and 9 MDS patients in MDS-201.

CML-203: A Phase II Open-Label Study of the Subcutaneous Administration of Homoharringtonine (Omacetaxine Mepesuccinate; OMA) in the Treatment of Patients with Chronic Myeloid Leukaemia (CML) Who Have Failed or Are Intolerant to Tyrosine Kinase Inhibitor Therapy

EudraCT Number: 2007-001286-15

First patient in: March 23, 2007

Status: Ongoing, data cut off was March 6, 2009

Methods/Treatment/Endpoints: identical with CML-202

In- and Exclusion: Failure or intolerance, or a combination of prior failure and intolerance to prior treatments with at least two TKIs (or with one TKI for patients enrolled in India, n=3)). Failure of TKI treatment may either have been primary (never achieved a response) or secondary resistance (loss of response). Intolerance to TKI treatment was defined as one of the following: Grade 3-4 non-haematologic toxicity that did not resolve with adequate intervention; Grade 4 haematologic toxicity that lasted more than 7 days; Any Grade ≥ 2 toxicity that was unacceptable to the patient. Other in- and exclusion criteria similar to CML-202.

Study population: A total of 65 patients were included into the ITT from 28 centres. (CML-CP n=30, CML-AP n=20; CML-BP n=15 with 18 patients (12 [40.0%] CML-CP patients and six [30.0%] CML-AP patients) still ongoing at data cut-off). The study started a year after CML-202, but less patients are still ongoing compared to CML-202 (CML-203 vs CML-202: 27.7% vs 36.4 %).

The reasons for discontinuation of study compared to CML-202 were less frequently due to disease progression (26.2 % vs 31.8%), death (7.7% - only in AP and BP vs 13.6%), AE (3.1 s 7.6%), but notably more frequently due to failure to achieve meaningful response (7.7 vs 3%), "other" (including e.g. transplant or lack of response) (15.4 vs 1.5%) or at the request of the patient/investigator/sponsor/regulatory agency. (12.3 vs 4.5%).

Baseline demographics: Compared to CML-202, patients in CML-203 were slightly younger (in particular CML-AP median age 52 years versus 62 years) and included a higher percentage of female (+17%) and non-Caucasian (+20%) patients. Only 5 patients were of ECOG 2-3.

CML disease characteristics and haematologic status at baseline The median time from initial CML diagnosis was 68.0, 102.7 and 44.1 months in chronic, accelerated and blast phase respectively.

Clonal evolution, an indicator of more advanced disease, was identified in 5 (16.7%) CML-CP, eight (40.0%) CML-AP and in 13 (86.7%) CML-BP patients.

As in CML-202, some patients were enrolled in ongoing CHR (CML-CP: n=6; CML-AP n=4; BP n=1) and/or concurrent HU treatment (CML-CP n=16; CML-AP n=10; CML-BP n=10). Baseline mutations in BCR-ABL were identified in a third of the total study population, but only n=49 had a baseline assessment available. The most common mutation were non P-loop mutations (n=10), P-loop mutations in seven (33.3%) and compound mutations (n=4). Two patients harboured the T315I mutation in one patient each in CML-AP and CML-BP.

Treatment history: Except for three CML-AP patients from India, all patients had been treated with at least 2 TKI before enrolment for at least one year with adequately escalated doses in the majority of patients. The majority fulfilled the inclusion criterion of failure to prior TKI and for many patients several failure types were reported. Two patients were noted to be intolerant, only. Overall, 50.8% patients were CHR-negative in spite of adequate HU treatment.

Primary efficacy analysis: The primary analysis of categorical classification of the best haematologic and cytogenetic response by disease phase, assessed by the independent DMC as reported by the applicant is presented in the table below:

Table 4 Best Haematologic and cytogenetic response by disease phase DMC classification in supportive trial CML-203

| Category/Statistic | Cohorts | | | Total (N = 65) |
|---|---------------------|-------------------------|-------------------|-------------------|
| | Chronic (N = 30) | Accelerated (N = 20) | Blast (N = 15) | |
| Overall hematologic response ^a | 24 (80.0%) | 15 (75.0%) | 8 (53.3%) | 47 (72.3%) |
| One-sided 95% lower confidence limit | 61.43% | 50.90% | 26.59% | 59.81% |
| Hematologic response categories | | | | |
| CHR | 24 (80.0%) | 12 (60.0%) | 6 (40.0%) | 42 (64.6%) |
| Unconfirmed CHR | NA | 1 (5.0%) | 2 (13.3%) | 3 (4.6%) |
| PHR | 2 (6.7%) | 0 | 0 | 2 (3.1%) |
| HI | 0 | 1 (5.0%) | 0 | 1 (1.5%) |
| RCP | NA | 3 (15.0%) | 2 (13.3%) | 5 (7.7%) |
| NEL | NA | 0 | 0 | 0 |
| No response | 3 (10.0%) | 3 (15.0%) | 5 (33.3%) | 11 (16.9%) |
| Unevaluable | 1 (3.3%) | 0 | 0 | 1 (1.5%) |
| Overall (any) CyR | 6 (20.0%) | 4 (20.0%) | 1 (6.7%) | 11 (16.9%) |
| MCyR ^a | 6 (20.0%) | 1 (5.0%) | 0 | 7 (10.8%) |
| One-sided 95% lower confidence limit | 7.71% | 0.13% | 0 | 4.44% |
| CyR categories | | | | |
| CCyR: 0% Ph + cells ^b | 1 (3.3%) | 0 | 0 | 1 (1.5%) |
| PCyR: > 0% - 35% Ph + cells ^b | 5 (16.7%) | 1 (5.0%) | 0 | 6 (9.2%) |
| Minor: > 35 – 65% Ph+ cells | 0 | 2 (10.0%) | 0 | 2 (3.1%) |

All patients with CHR at base-line maintained a CHR irrespective of concomitant HU treatment. Response rate in patients with baseline or on study treatment with HU appear numerically lower compared to patients not requiring HU. Compared with CML-202, the quality of achieved response appears lower in view of higher proportion of partial or transient responses.

Secondary efficacy analysis : Haematologic response was achieved in the majority of patients during the first treatment cycle and in within 8 days for 25% of patients. All responses were achieved within 4 treatment cycles regardless of disease phase. Some molecular responses (10%) were observed among CML-CP patients. For duration of response and cumulative dose, a high standard deviation and range for mean and median, respectively are observed. Follow-up for survival ended with study discontinuation resulting in a high rate of early censoring.

Table 5 CML-203 Secondary efficacy endpoints per disease phase

| | Chronic (n=30) | Accelerated (n=20) | Blast (n=15) |
|---|---------------------------|-------------------------------|--|
| Duration of overall haematologic response (months) | | | |
| N | 24 | 15 | 8 |
| mean (SD) | 5.4 (3.4) | 4.2 (2.9) | 4.0 (3.1) |
| median (range) | 4.7 (1.4-13) mo | 2.5 (1.8-10.5) | 2.8 (1.6-11) |
| Duration of major cytogenetic response (months) | | | |
| N | 6* | 1 [§] | 0 |
| mean (SD) | 1.6(1.1) | 2 days | 0 |
| median (range) | 1.6 (0.0 -2.9) | 2 days | 0 |
| Overall survival | | | |
| N | 30 | 20 | 15 |
| deaths on study | 0 | 2 | 4 |
| median OS (months) | NA | NA | 14.5 (95% CI: 3.1 - 14.5) (one patient at risk, only) |
| Progression[§]-free survival | | | |
| Median (95% CI) months | 11.1 (95% CI: 5.9 -NA) | 5.7 (95% CL 3.6-NA); | 2.6 (95% CI: 2.0, 2.8) |

* two confirmed; 4 unconfirmed; 5 ongoing a data cut-off § unconfirmed, ongoing \$ definition unclear

Single patients as illustrative examples for inconsistencies or contradictions in the dossier

A. Favouring negative benefit/risk conclusion

1. Unclear necessity of treatment with highly cytotoxic treatment
 - a) CML-202: One patient with ongoing CyR (20% Ph+) and contradictory information on CHR
2. Inconsistent or contradictory baseline assessment
 - a) CML-202: In table 11.2.5 and in appendix 16.2.4.1, 8 patients are reported as being in CHR at the time of enrolment. Inconsistent and contradictive information is available in the DMC spread-sheet given in listing 16.4.2. The listings only agree with respect to 4 patients, while up to 16 of 40 CML-CP patients are in CHR at baseline, if both listings are considered. Conflicting information between DMC (appendix 16.4.2) and appendix 16.2.4. Also concerns several patients, who will be later listed as patients achieving major cytogenetic response.
 - b) CML-202: e.g. for one patient (confirmed CCyR at visit 3, 5 and 6): According to appendix 16.2.6.2, no baseline cytogenetic analysis was performed (waived? but not found!) and the first cytogenetic response for this patient is classified as CCyR.
 - c) CML-202: In the narrative for a patient, implausible start and end dates for CCyR to preceding treatment are found (Start: 08DEC2005-End: 07DEC2005). According to listing 16.2.6.2, 20% Ph+ metaphases are demonstrated for this patient.
 - d) CML-202: For one patient - baseline cytogenetic data available? For another patient, cytogenetic information dating from d-116 only?
 - e) CML-202: For 5 patients: at least minimal cytogenetic response at baseline
3. Unreliable information on actually administered doses:
 - a) CML-202: For one patient: Missed doses reported in the narrative are imputed for cycle analysis in appendix 16.2.5.3 resulting in anticonservative bias.
This example raises concern with respect to the validity of registering applied doses.
4. No obvious patient benefit with achievement of primary endpoint:
 - a) CML-202: A patient is listed as having confirmed CHR in spite of developing bone marrow failure for which he will be discontinued.
 - b) CML-202: A patient entered the study in ongoing CHR (according to narrative and listing 16.2.4.1, but listed as CHR-negative in DMC spread sheet) and received a single cycle of omacetaxine until December 3 2008. Subsequent cycle had to be delayed due to ongoing SAE grade 3 and 4 until cut-off in March 2009. This patient is counted as patient in ongoing CHR of a duration of 3.52 months.
 - c) CML-203: A patient was treated for a single cycle with omacetaxine and achieved CHR on study day 7. According to listing 16.2.1., this patient discontinued study CML-203 for excessive grade 3/4 toxicity in the absence of a meaningful response.

- d) CML-202: For one patient: CP with prior HU without achieving CHR Duration of response: 2.14 months (1/2 while in grade 4 aplasia)
- e) CML-202: A CP patient is another example for the questionable risk/benefit and suboptimal dose-selection: Ten of 16 cycles for the patient had to be delayed (3.cycle 105 days, 4.cycle 34 days, 5. cycle 53 days etc.). While reason for delay for 105 days (> 3 x cycle length!) is reported as "other AE or grade 3 diarrhea" in several listings, (e.g. narrative, 16.2.5.3), after laborious reconstruction of events, a grade 4 thrombocytopenia and neutropenia can be determined as likely additional reason for delay. The subsequent 7 cycles are all delayed for pancytopenia (narrative) and the maintenance dose has to be reduced to 4 dosing days in order to avoid further delays. Duration of response spans the entire treatment period including recovery times from pancytopenia.
- f) CML-202: A responding patient discontinues due to "excessive grade 3-4 toxicity without response/clear efficiency of treatment" (according to listing 16.2.1). However, the hematotoxicity is counted as response which is then censored at the time of study discontinuation, i.e. the waiting time for recovery from myelosuppression is considered a response.
- g) CML-202: Patient reported with grade 4 thrombocytopenia after 1st cycle but included as responder for 3 subsequent months in the absence of further treatment
- 5. Implausible or unreliable response assessment
 - a) CML-202: A patient in BP "achieves" RCP on study 1. This is suggestive of a misclassification of phase rather than response to omacetaxine. This patient contributes to the duration of response by 1.2 months until his death in the ICU due to sepsis, possibly related to omacetaxine.
 - b) CML-202: One Patient in CP and 2 patients in AP are listed as having molecular responses in spite of not having obtained a cytogenetic response, suggesting a laboratory artefact. The sample of another patient in which a molecular response was determined was commented on as "suboptimal quality".
 - c) CML-202: when both control genes are used for one patient, results are not necessarily concordant, e.g. a patient had analysis at day 92 and 259. The sample demonstrating MMR for another patient 005/001 is described as "suboptimal quality".
- 6. Insufficient follow-up
 - a) CML-202: For a patient: Study discontinuation due to grade 4 aplasia. Last contact (long before data cut-off) is the day of discontinuation. Neither SAE status nor survival status is updated.
 - b) CML-202: A patient had no entry in narrative since Nov 2008 (according to listing 16.2.1).
- 7. Relevant protocol violators
 - a) CML-202: One responding patient in CP (CHR, CCyR and MMR) received cyclophosphamide and taxane as breast cancer treatment during the study (d120-d183). For a conservative assessment of the ability of omacetaxine to maintain responses, this patient should be excluded from the analysis of duration of response.
 - b) CML-203: A BP patient received only one cycle of omacetaxine during the first month of study participation after which infiltration of the CNS required intrathecal treatment. Conflicting information is reported in the narrative with study discontinuation either in March 2008 or October 2008.

B. Highlighting high intra-individual variability

- 8. Selection of subset benefiting more than the average
 - a) CML-202: At the present time, 4 patients (10%) have received more than 16 cycles of treatment (3 x the median!). Immaturity of data does not yet allow conclusions (55% of CP patients are still ongoing) .

Discussion on clinical efficacy

Omacetaxine is a semisynthetic version of homoharringtonin, a plant alkaloid. The late-line indication sought is a molecular subset of an orphan indication "TEKINEX is indicated for the treatment of adults with Philadelphia chromosome positive chronic myeloid leukaemia who have the Bcr-Abl T315I kinase domain mutation and who are resistant to prior imatinib therapy." Omacetaxine is not specific for T315I positive patients, but has a general and currently insufficiently described mechanism of action. In view of the rarity of the mutation, an uncontrolled trial was agreed on with the SAWP as long as compelling evidence on a positive benefit/risk balance would be available.

The pivotal study CML-202 evaluated omacetaxine in sixty-six patients with T315I mutations previously treated with at least imatinib, but the majority had received treatment with at least two TKIs. The T315I mutation was a requirement for inclusion and the proposed indication is restricted to this population. However, one third of the patients had their mutations not confirmed by reference laboratory. Out of those 10 patients (15%) were even tested negative by the reference lab. As in some studies the mutation is described to be transient, this is of concern.

Patients in chronic phase form the majority of the study population (40 of 66 in the pivotal study, 30 of 65 in relevant supportive study CML-203). The medical need is highest in accelerated phase and blast phase. A demonstration of a relevant patient benefit with an acceptable toxicity for patients in chronic phase is therefore considered critical for this application. Treatment of patients in the more manageable chronic phase usually aims at avoiding selection of drug-resistant clones or detrimental effects on subsequent treatment success in the more advanced accelerated or blast phase.

In study CML-202, an overall haematologic response (CHR) was achieved by 34 of 40 CML-CP patients for a minimum of 8 weeks, out of those eight were in CHR already at baseline. The median duration was 7.7 months (1.7-23.6). In accelerated phase and blast phase, the responses were limited both with regards to numbers and duration. Five accelerated phase and 2 blast phase patients achieved a CHR with median durations of 3.9 (1.7-14.8) and 2.2 (1.2-4.4) months respectively. All CHR were achieved within 3 treatment cycles.

Among the chronic phase patients, 6 patients achieved a MCyR out of which 4 were CCyR. The median duration was 6 (0.8-16.1) months. One-third of the cytogenetic responses were not confirmed. There were no cytogenetic responses in blast phase and only one in accelerated phase lasting for 1.9 months.

Depending on which house-keeping gene was used 2-6 chronic phase patients and 1-2 accelerated phase patients had a major molecular response.

For chronic phase patients a median overall survival time could not be calculated at the time of data cut off. The five deaths occurred early in the study (4 non-responders, one responder). In accelerated phase the median overall survival time was 18.8 months. Four of the 16 patients died. In blast phase patients the median overall survival time was 1.8 months; seven of the 10 patients died. There was no information given regarding treatments post study. The overall survival is limited especially in blast phase.

The study CML-203, there were slightly more haematologic responses in accelerated and blast phase; in the chronic phase the frequency of CHRs was similar to CML-202. The median durations of responses were shorter in chronic and accelerated phase and similar in blast phase (4.7 , 2.5 and 2.8 months respectively). The frequency of MCyR was similar, with responses in 6 chronic patients and 1 accelerated phase patient. However the duration was very short with a median of 1.6 and 0.007 months respectively. The majority of the responses were not confirmed. Three of the chronic phase patients achieved a major molecular response. Compared to CML-202 there was a longer overall survival in the accelerated and blast phase patients, which tentatively could be due to the extent of transplantations in CML-203, but also to a tentatively worse prognosis in the mutated population.

Results as presented by the applicant (with inconsistencies or contradictions) do not allow firm conclusion: it is currently unclear to what extent omacetaxine contributes to response achievement or whether it mainly maintains already established responses at the expense of considerable toxicity.

Most important findings and deficiencies:

Suboptimal dose selection

Dose finding for the pivotal and supportive trial is regarded as suboptimal. It appears that the proposed posology was only used in a minority of patients, indicating large intra-individual variability. Prolonged dose interruptions and a high percentage of long-term transfusion-dependent patients were observed. More detailed analyses are required.

Baseline characteristics

Inconsistencies were found with respect to baseline status of CHR and a discussion of baseline cytogenetic response was not found. Clarification is required as these are relevant data for efficacy assessment.

Diffuse composite endpoint

For the present MAA, it is important to distinguish clinically meaningful response to treatment accompanied by patient benefit from hematotoxicity – since both outcome assessments are practically based on the same parameters (blood counts). A more conservative assessment of response achievement and response duration assessment is required. While complete normalisation of haematopoiesis may not be expected from an unselective inhibitor protein synthesis, excessive hematotoxicity is not associated with obvious patient benefit.

Survival endpoints

While the SAWP agreed that OS as primary endpoint may be unfeasible in chronic phase patients, analysis of survival was proposed for patients in AP or BP. Follow-up on overall survival in both relevant trials is insufficient since the method of censoring in trials CML-202 and CML-203 may be subject to strong bias. Patients are censored at the day of study discontinuation and no follow-up on subsequent treatment (success) or survival is reported. Not even patients who discontinue the study due to excessive toxicity appear to have been followed-up for survival. Exclusion of a detrimental effect on survival is a prerequisite for a positive benefit/risk evaluation.

Inconsistencies and contradictions

A number of inconsistencies with respect to baseline, response assessment and efficacy in the presence of considerable toxicity have been observed. These inconsistencies need to be clarified.

SPC issues

The posology proposed by the applicant in section 4.2 of the SPC corresponds in most parts to the treatment as planned for the clinical trial. Section 4.2 seems therefore insufficiently justified and neither section 4.4 nor section 4.8 or 4.9 of the SPC adequately summarise the experience from the pivotal studies.

Section 4.4 also does not appropriately reflect the pivotal study. Prophylaxis for tumour lysis syndrome is not mentioned.

The recommendation for biweekly monitoring for a self-administered cytotoxic drug given in an out-patient setting does not reflect the critical side-effects observed in practice (clinical trials, compassionate use program).

Agreement of results

A comparison of the pivotal study CML-202 with the supportive trial CML-203 is regarded as premature since a number of issues needs to be clarified. The most notable agreement of the data at the present time is the observation that in both studies, a small subset of patients appears to tolerate treatment

with omacetaxine much better compared to the average. This highlights the inappropriateness of summary statistics (mean, median) for the evaluation of results and necessitates a more sophisticated presentation of data. In view of the relatively low number of patients included, the applicant is asked to consider to present individual data as e.g. scatterplots.

Cross-trial comparison

Current treatment options for this population are limited to those of the pre-TKI era, since the mutation confers resistance to all authorised TKIs. Historical data on efficacy of these historical treatment options such as anthracyclins, amsacrine or cytarabine are, however, of limited value for the present evaluation since, first, the pre-treatment history (both type and duration) largely differs from contemporary patients and, second, the impact on the mutation on prognosis is not firmly established.

Still, the comparison interferon/cytarabine data from the IRIS study, where imatinib was compared to low dose cytarabine/ interferon in chronic phase patients is presented below. This was first-line treatment as opposed to the studies in the application where the patients were much more heavily pretreated. In the interferon/cytarabine group after a median follow-up of 19 months, an estimated rate of a major cytogenetic response 34.7 percent (95 percent confidence interval, 29.3 to 40.0) was recorded. The estimated rates of complete cytogenetic response was 14.5 percent (95 percent confidence interval, 10.5 to 18.5), respectively. At 18 months, the estimated rate of freedom from progression to accelerated-phase or blast-crisis CML was 91.5 percent in the combination-therapy group (1)

Furthermore follow up data for patients with T3151 mutations in a retrospective study showed, when analysing medical records from 222 patients from 9 countries a median OS from T315I mutation detection of 22.4, 28.4 and 4.0 months in CP, AP and BP respectively. The PFS was 11.5, 22.2 and 1.8 months respectively. Patients were treated with (in decreasing frequency) 2nd generation TKIs, hydroxyurea, imatinib, cytarabine, stem cell transplantation, allogeneic transplantations MK-0457, other investigational agents and IFN (2). In view of the shorter OS and PFS in the group of patients with chronic phase CML, selection bias limits the interpretability of results.

Conclusions on clinical efficacy

Results as presented by the applicant currently do not convincingly demonstrate efficacy. The responses are mainly haematologic and seen in the chronic phase patients. Due to the low number of patients, efficacy data in CML-BP and CML-AP are currently considered as less robust in the pivotal population.

It is currently not possible to sufficiently differentiate between haematological response and unspecific haematotoxicity. The results both with regards to responses and overall survival at least in the group with worst prognosis and the largest medical need do not give the impression that the course of the disease is markedly changed.

Clinical safety

Omacetaxine (OMA, respectively HHT, homoharringtonine) is derived from Chinese traditional medicine and investigated since more than 30 years in several haematological and oncological indications. Class effects are not known since the cetaxine omacetaxine or HHT is the first of this class of plant alkaloids.

Non-clinical studies indicated that omacetaxine is toxicologically very potent, with a high lethality in animals and has very narrow safety margin. Toxicological effects are mainly attributed to antiproliferative pharmacological activity, but effects independent of the pharmacological activity are also possible, like hepatotoxicity and cardiotoxicity.

As in other cytotoxic agents used in oncology, safety data is only available from patients because the significant product toxicity precludes any inclusion of healthy volunteers in clinical studies.

Furthermore, the pivotal trial was performed in a small number of patients (orphan indication) and other information derives exclusively from pilot studies performed in several other haematological indications (please refer to table IV.1 in the AR). All studies discussed are small uncontrolled with highly heterogeneous patient population.

Early studies with HHT explored different schedules, routes of administration and combination partners. Serious cardiac events (arrhythmias and hypotension) were often observed and were dose limiting when administered using bolus or short intravenous (IV) infusion schedules. Subsequent studies in leukaemic indications demonstrated some activity either as a single agent or in combination. There was no significant activity in solid tumours. Lower doses and longer exposure schedules reduced hypotension and cardiotoxic events, with the establishment of myelosuppression as dose-limiting toxicity.

The applicant focused on the discussion of safety populations (study group 1 and 2) which are pooled from different trials.

Study group 1: * all patients who were treated with omacetaxine regardless of way of administration and dosing regimen.

*data presented for all patients independent from disease phase

Study group 2: * patients from CML-202 or CML-203

*data presented individually for patients by disease phase

By the applicant, results from the pooled safety populations are not compared or discussed with respect to the safety population from the pivotal trial CML-202 which is at the end the most relevant for this application.

Patient exposure

Exposure data with omacetaxine are highly heterogeneous with a high relative frequency of extreme values, i.e. considerable subgroups of patients on the one hand discontinuing early or, on the other hand, continue treatment for much longer than the average. The difference in maturity of the data with much shorter follow up in the supportive trial CML-203 compared to CML-202 (exposure data available for more than 12 mo: CML-202 23% compared to only 5% of patients in CML-203) also impact on the summary statistic.

Another consistently observed phenomenon is that treatment had to be delayed in some patients repeatedly (median 3 x, range 1-11 in the pivotal study) and for considerable duration (up to 184 days), while other patients tolerated treatment well without notable dose delays or dose reductions. However, in view of the missing data imputation, more information is required in order to rule out notable overestimation of compliance (see efficacy section).

Table 7 illustrates the heterogeneity of exposure with respect to data source (individual trial or study group defined by the applicant) or disease phase.

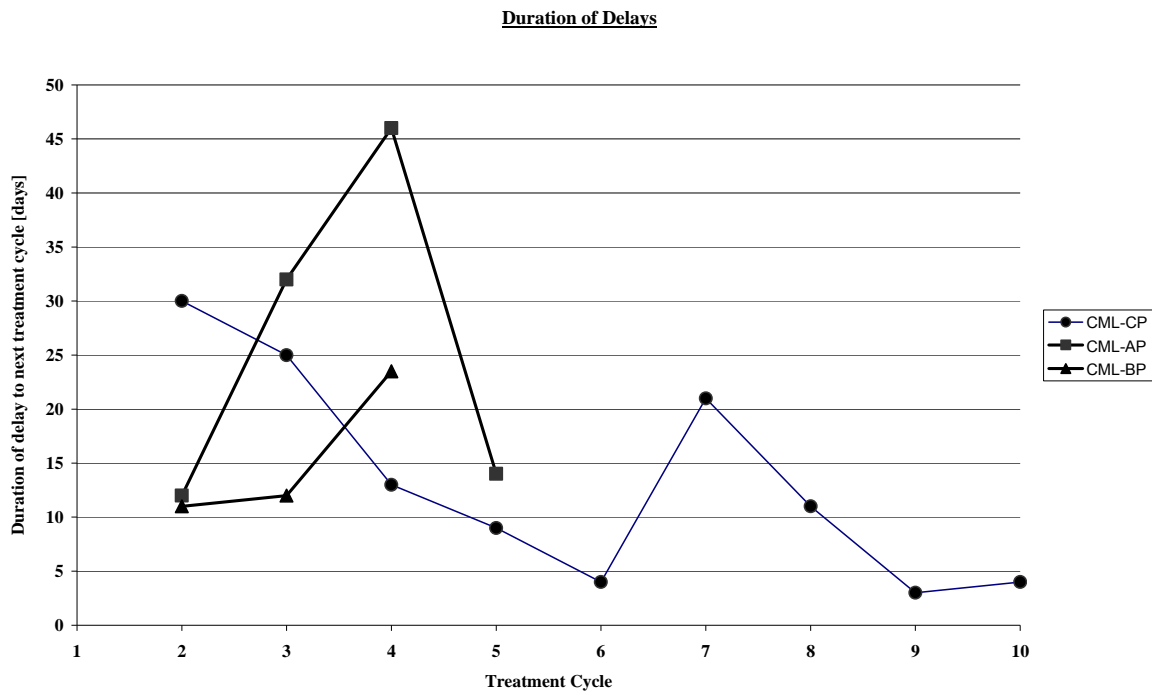
Table 6 Summary of exposure data

| | Safety population of the pivotal study CML-202 n=66 | Safety population group 1 n=212 (no information per phase found) | Safety population group 2 (CML-202-203) n=131 |
|--|--|---|---|
| Median total duration of exposure to omacetaxine [mo] (range) | 4.4 mo (0.1 - 28.9) CP: 6.8 mo (0.5 - 28.5) | 2.4 months (0.1-29.1) | 3.3 months (0.1 - 28.9) CP: 5.4 (0.3-28.9) |
| Mean (SD) duration of exposure [mo] | 6.7 (7.00) CP: 8.6 (7.2) | (5.52) months | 5.3 (5.67) months CP: 6.9 (6.32) months |
| Median total dose delivered [mg/m ²] (range) | 100.6 (7.6-614.9) CP: 119.4 mg/m ² (34.8 -355.6) | 70.4 mg/m ² (6.3-614.9) | 90.8 mg/m ² (7.6- 614.9) CP: 105.1 (20.1 - 355.6) |
| Mean (SD) total dose | 128.4 (105.67) CP: 147.8 (90.4) | 95.7 mg/m ² (83.06) | 116.3 mg/m ² (91.90) CP: 129.3 (81.58) |
| Median number of treatment cycles (range) | 4 (1 - 25) CP: 5.5 (1-25) | 3 (1-25) | 3 (1-25) CP: 5 (1-25) |
| Mean (SD) number of treatment cycles | 6 (5.8) cycles CP: 7.4 (6.1) | 4 cycles (4.2) | 5 cycles (4.7) CP: 6 (5.2) |
| Number of patients with delays to treatment cycles | 41 of 54 patients (76%) * 45% to 56% through Cycle 1 to 4: CML-CP: 51 - 78% CML-AP: 42 - 60 % CML-BP: 40 -100 % | n=103 (denominator not clear since information on how many patients received >1 cycle not found) | n=78 of 107 patients with > 1 cycle (73 %) through Cycle 1 to 4: CML-CP: 51 - 78% CML-AP: 29 - 60 % CML-BP: 25 -100 % |
| Median number of delays in study | 3 (1-11) | 2(1-11) | 2(1-11) |
| Median days of cycle delay based on median length of delay per patient | 11(1-89) | 11(1-89) | 12(1-89) |
| Range of Medians + overall Range of duration of delays (cycle 1-4) | CP: 13-30 (1-184) AP: 12-45 (1-74) BP: 11-23.5 (4-39) | information not found | range: CP: 1-184 AP: 1-74 BP: 4-51 |

* n=12 patients in 202 received only one cycle, delays are therefore not applicable

Delays are more frequent and last longer in earlier cycles (usually induction cycles) compared to later cycles (usually maintenance) and can be seen in the following graph:

Figure 1 Median of Duration of delay in patients with delays in the pivotal study CML-202



Toxicity-guided individual dosing replaced the recommended posology in the pivotal and supportive trials. Dose reductions were not addressed by the applicant and potential consequences for safety aspects were not discussed. No evidence and proposal for improvement of patient's safety by changes for instance in patient's monitoring in the outpatient setting were derived from the study and discussed.

Adverse events

Treatment of omacetaxine is accompanied by a high number of adverse events. In view of the outpatient setting underreporting of TEAEs is likely. Only adverse events volunteered by the patients or note by the staff during the monitoring visits) were reported.

In the pivotal study 65 of 66 patients (98.5%) reported at least one TEAE. In 61 of these, at least one TEAE was considered to be related to omacetaxine (i.e., possibly related, probably related, or unknown or relationship not specified). Rate of adverse events were comparable in the different disease phases, considering the different duration of exposure according to disease phase (97.5% CML-CP, 13 (81.3%) CML-AP and 9 of 10 CML-BP patients). Observations are similar in the combined analysis of CML-202 and CML-203.

Most of the TEAEs in the pivotal trial were reported in the following SOC:

59/66 patients (89.4%) General disorders and administration site conditions

51/66 patients (77,3%) Blood and lymphatic system disorders

51/66 patients (77,3%) Gastrointestinal disorders

38/66 patients (57,6%) Skin and subcutaneous tissue disorders

31/66 patients (47,0%) Infections and infestations (31 patients; 47.0%)

31/66 patients (47%) Respiratory, thoracic and mediastinal disorders

29/66 patients (43,9%) Musculoskeletal and connective tissue disorders

27/66 patients (40.9%)Metabolism and nutrition disorders

a) TEAEs in Blood and lymphatic system:

Overall, hematotoxicity is the most relevant toxicity for Omacetaxine as shown in Table 8 Myelotoxicity respectively hematotoxicity was demonstrated in a total of 48 patients (72.7%) (33 [82.5%] CML-CP, nine [56.3%] CML-AP, and six [60%] CML-BP) in the pivotal study CML-202. This is finding is overall consistent with the safety results of the safety group 2 analysis which reports TEAEs out of hematotoxicity in 99 (75,6%) patients, in detail in 58/70 (82,9%) of CML-CP patients, 25/36 (69/4%) of CML-AP patients and in 16/25 (64%) of CML-BP patients. This demonstrates overall consistent high rate of the TEAEs.

Table 7: TEAEs in Blood and Lymphatic system regarding Preferred Term

| TEAE | CML-CP | | CML-AP | | CML-BC | |
|---|-----------------|----------------|----------------|----------------|----------------|----------------|
| Study population | Pivotal | Group 2 | Pivotal | Group 2 | Pivotal | Group 2 |
| | CML202 | CML202 | CML202 | CML202 | CML202 | CML202 |
| | N=40 | +203 | N=16 | +203 | N=10 | +203 |
| | | N=70 | | N=36 | | N=25 |
| Blood and lymphatic system disorders | | | | | | |
| Anaemia | 30/75,0% | 44/62,9% | 6/37,5% | 13/36,1% | 1/10% | 5/20% |
| Thrombocytopenia | 29/72,5% | 49/70,0% | 7/43,8% | 18/50,0% | 4/40% | 9/36% |
| Neutropenia | 20/50,0% | 36/51,4% | 4/25% | 5/13,9% | 4/40% | 7/28,0% |
| Febrile | 5/12,5% | 5/7,1% | 4/25% | 6/16,7% | 3/30% | 6/24% |
| Neutropenia | | | | | | |
| Lymphopenia | 7/17,5% | 8/13,5% | 0 | 0 | 0 | 0 |
| Bone marrow | 4/10% | 8/11,4% | 1/6.3% | 0 | 0 | 0 |
| failure | | | | | | |
| Pancytopenia | 2/5%? | 3/ 4,3% | 2/12,5% | 3/ 8,3% | 0 | 1/ 4% |

Comparable high numbers of Serious AEs in blood and lymphatic system indicates a consistent high risk for severe haematotoxicity during use of Omacetaxine, which is detectable from all non-clinical and clinical studies performed before. It should be noted that overall a trend was detectable in the pivotal trial that haematotoxicity was most pronounced in the target population with CML-CP.

In CML-CP patients a trend can be observed for a difference between ~ 70% rates for thrombocytopenia and anaemia compared to a probably lower~50% rate for neutropenia. This finding might be discussed as a signal for differential toxicity to different cells lines in haematopoiesis and might indicate that thrombocytopoiesis as well as the red cell precursors are more pronounced affected by Omacetaxine than granulocytopoiesis. However, this finding might also be interpreted as a finding by chance in a small population or as a result of disease immanent conditions in CML.

b.) Other treatment-emergent adverse events (TEAEs):

From the limited information reported no final comparison between safety group 2 and the target population can be performed with regard to other TEAEs, because some data is not available from the study report. Out of the already mentioned unacceptable form of data reporting/analysis, the relationship with the treatment, causality or duration respectively reversibility cannot adequately be assessed. At this level of assessment it can be concluded that the frequency of other TEAEs in the CML-CP subgroup is comparable between the pivotal safety group and safety group 2. As already mentioned underestimation of TEAEs is presumed. Frequency of TEAEs highly susceptible for hematotoxicity associated complications like infections or bleedings are lower as expected. They might be underrepresented, as patients have been treated as outpatients and no systematic evaluation of TEAEs was included in the study protocol. Insofar, the overall validity of the TEAE data seemed to be limited, in particular with regard to lower grade TEAEs. Thus, the SAEs reported and the objective laboratory results might be more representative for the assessment of other important safety concerns than the information on overall TEAEs.

Gastrointestinal TEAEs and general disorders TEAEs, in particular regarding reactions at the injection site, are the most frequent reported TEAEs indicating further relevant toxicity.

Diarrhoea was the most reported event beside haematological TEAEs. But, as not differentiation between diarrhoea of infectious origin and other forms (mucositis ?) was performed or reported, it cannot be excluded that some of these events are undetected infections and thus also might be resulting as complication of hematotoxicity.

With regard to the injection site TEAEs, which occurred in about 10 to 15 % of the patients, it should be noted that rash/ erythema in association with pruritus can be interpreted as local toxicity, however, might also be indicative for allergic reactions. No SAEs were reported concerning these TEAEs, but one patient developed a severe cellulitis.

Non-haematologic adverse events of special interest are cardiovascular events, hyperglycemia, hepatotoxicity and potential renal toxicity.

Serious adverse events

It is worthwhile to mention as one of the rare positive findings in this application that overall non-haematologic toxicity seems to be low from the TEAEs and SAEs reported and manageable, even in the context of probably underreporting of adverse events. However, this is a preliminary statement and again further analysis has to be performed on more mature data. Unfortunately, no quality of life data are available from the clinical trials, which again make the weighting of such a potential advantage more difficult, in particular in an open uncontrolled study.

Otherwise, it is consistently demonstrated (please refer to Table 9) that the rates of overall SAEs, deaths and SAEs related to omacetaxine are at the highest in the pivotal trial CML-202 and significantly lower in both safety groups predefined by the applicant, which indicates improper dilution of findings in the target population. A clear underestimation of risks associated with omacetaxine is expected, if the applicant's view on safety would be uncritically applied. Only the safety data of the pivotal trial CML-202 generated in the target population applied seemed to reflect adequately the potential specificities of the target population. Differences to other CML population and source of bias in clinical studies are described and discussed in the literature (e.g. Nicolini, 2009).

Table 8: Overview about Serious adverse events in the different safety groups defined by the applicant and in the pivotal study CML-202:

| | Safety Group 1 N=212 | Safety Group 2 N=131 | Safety Pivotal study (CML-202) N=66 |
|---------------------------|---------------------------------------|---------------------------------------|--|
| Overall SAEs | 48,1 % | 55,7% (N=73/131) | 65,2% (N=43/66) resp. 72.7 % |
| Deaths | 16,0 % (N=34) | 16,8% (N=22/131) | 24,2% (N=16/66) |
| SAE related to OMA | 29,3 % | 32,8% (43/131) | 40.9% (N=27/66) |

Table 10 provides an overview about the severity of SAEs observed in study CML-202 and safety group 2

Table 9: Overview about Treatment emergent Adverse Events, Serious Adverse Events in safety group 2 and the pivotal study with regard to disease phase (CML-CP,AP and BP)

| | Patients with TEAEs | | TEAE Grade 3 | | Total SAEs | | SAE Grade 4 | | SAE Grade 5 (deaths) | |
|---------------|----------------------------|-----------------------|---------------------|-----------------------|-------------------|-----------------------|--------------------|-----------------------|-----------------------------|-----------------------|
| | CML-202 | Safety group 2 | CML-202 | Safety group 2 | CML-202 | Safety group 2 | CML-202 | Safety group 2 | CML-202 | Safety group 2 |
| Total | 98,5 | 96,9% | N/A | N/A | 65,2 % | 55,7% | N/A | N/A | 24,2 % | 16,8% |
| CML-CP | 97,5 % | 97,1% | 22,5 % | 30,0% | 60% | 48,6% | 57,5 % | 52,9% | 12,5 % | 7,1% |
| CML-AP | 100% | 94,4% | 18,8 % | 19,4% | 62,5 % | 52,8% | 37,5 % | 47,2% | 25% | 16,7% |
| CML-BP | 100% | 100% | 10% | 16,0% | 90% | 80,0% | 20% | 32,0% | 70% | 44% |

The following information is available from the applicants' analysis and reports:

Serious AEs in Safety-Group 1:

Serious AEs were reported for 48.1% of the 212 patients in Study Group 2, and the percentage of patients with SAEs considered related to Omacetaxine was 29.2% according the applicants statement.

The most frequently reported SAEs (reported for 5 or more patients in Study Group 1 were primarily myelosuppressive events: thrombocytopenia (20 patients), febrile neutropenia (18 patients), anaemia (9 patients), disease progression (9 patients), bone marrow failure (8 patients), febrile bone marrow dysplasia (6 patients), pancytopenia (5 patients), and pneumonia (5 patients).

Serious AEs in Safety-Group 2:

Serious AEs were reported for a total of 73 patients (55.7%): 34 (48.6%) CML-CP patients, 19 (52.8%) CML-AP patients, and 20 (80.0%) CML-BP patients.

Serious AEs were most commonly reported in the

blood and lymphatic system disorders system (41 patients; 31.3%):

- thrombocytopenia (15 patients; 11.5%)
- febrile neutropenia (14 patients; 10.7%)
- bone marrow failure (eight patients; 6.1%)
- anaemia (six patients; 4.6%)
- febrile bone marrow aplasia (three patients; 2.3%)

- neutropenia (three patients; 2.3%)
- pancytopenia (three patients; 2.3%)
- blast cell crisis (two patients; 1.5%).

Other SAEs reported in more than one patient included the following:

- o disease progression (seven patients; 5.3%)
- infections
 - o pneumonia (four patients; 3.1%)
 - o diarrhoea (four patients, 3.1%)
 - o pyrexia (three patients, 2.3%)
 - o transfusion reaction (three patients, 2.3%)
 - o *death (two patients, 1.5%) ???*
 - o fatigue (two patients, 1.5%)
 - o cellulitis (two patients, 1.5%)
 - o sepsis (two patients, 1.5%)
- pulmonary haemorrhage (two patients, 1.5%)
- arrhythmia (two patients, 1.5%)
- subdural haematoma (two patients, 1.5%)
- convulsion (two patients, 1.5%)
- back pain (two patients, 1.5%)
- hypercalcaemia (two patients; 1.5%).

32,8 % (43/77) of the patients (32.8%) (28 [40%] CML-CP, nine [25.0%] CML-AP, and six [24%] CML-BP) had at least one SAE related to Omacetaxine regarding the investigator's judgment.

24.4% (32/131) of patients had TEAEs that were considered severe and 47.3% (62/131) of patients had TEAEs that were classified by the investigator as life-threatening. The incidence of haematologic toxicity was 68.7% .

Serious AEs were reported for 55.7% of the patients, and the incidence of SAEs considered related to omacetaxine was 32.8%.

7 (5.3%) patients discontinued study participation due to AEs

20 patients (15.3%) had TEAEs reported to have a fatal outcome

Serious AEs in the pivotal study CML-202:

Grade 3/4 TEAEs were reported for a total of 53 (81.5%) patients including 25 (83.3%) CML-CP patients, 15 (75.0%) CML-AP patients, and 13 (86.7%) CML-BP patients. Across the three disease phases, again most of the Grade 3/4 TEAEs were in blood and lymphatic system disorders 22/66 [73.3%].

Serious AEs were experienced by a total of 43 patients (65.2%) (24 [60%] CML-CP, 10 [62.5%] CML-AP, and nine [90%] CML-BP). SAEs regarding the investigator's judgement were considered to be related to Omacetaxine in a total of 27 patients (40.9%) (17 [42.5%] CML-CP, six [37.5%] CML-AP, and four [40%] CML-BP). Again hematotoxicity was most common.

In summary, as in TEAEs most SAEs occurred in the blood and lymphatic system disorder and in the group of non-haematological SAEs also a majority might indicate associated complications e.g. infections and bleedings. Only in 4 of the 73 SAEs observed in safety group 2 a relation to haematotoxicity respectively the underlying disease seems to be excluded per se with certainty from the type of complication observed: Hypercalcaemia, convulsion, arrhythmia, 'back pain

In general, it is acknowledged that drug-induced myelotoxicity may trigger transfusions and management of patients in advanced stage, especially with CML-AP and BP often includes transfusions

as consequence of the disease itself. However, **transfusions** were not analysed or further discussed in the Summary of Clinical Safety document and only a sparse summary is available. The following information from Study CML-202 is available:

CML-CP Patients:

Twenty-nine of 40 (72.5%) of CML-CP patients enrolled required transfusions during their study participation. In total, 296 transfusions were administered during the study; platelets constituted 49% of transfusions and red blood cell constituted 42% of transfusions. The remaining transfusions were of whole blood or other.

CML-AP Patients

Thirteen of 16 (81.6%) CML-AP patients enrolled required transfusions during their study participation. In total, 114 transfusions were administered during the study; platelets constituted 39% of transfusions and red blood cells constituted 49% of transfusions. The remaining transfusions were of whole blood or other.

CML-BP Patients

Eight of 10 (80%) CML-BP patients enrolled required transfusions during their study participation. In total, 235 transfusions were administered during the study; platelets constituted 52% of transfusions and red blood cells constituted 40% of transfusions. The remaining transfusions were of plasma.

As total dose exposure and number of cycles in CML-BP patients was limited, we could agree with the applicant's view that the administered transfusions in this subpopulation may be considered as part of the disease management, and not mainly as the consequence of the drug toxicity. However, as the need of transfusions reflects also the high rate of SAEs in blood and lymphatic system it will at least partially indicate the severity of myelotoxicity due to Omacetaxine.

The highest rate of transfusions was observed in the CML-AP (81%) population, in which disease immanent bias might be more present than in CML-CP, but exposure seems overall to have been higher than in CML-BP. In this context, only a little lower need for transfusions in 72.5 % of the CML-CP patients seem to be more indicative for a relevant haematotoxicity of Omacetaxine. This suspect is further substantiated by the high rate of 49% of platelet transfusion in CML-CP patients, which may be interpreted as more indicative for a drug-related myelotoxicity.

In general, transfusion of platelets is more critical than transfusion of red cells. Refractoriness due to antibody formation occurs very often and handling of this complication is significantly more difficult than in red cells. Insofar, the high need of platelets in CML-CP patients raises particular concerns, as they might become refractory to platelet transfusion at the time of further disease progress, when high level of cytotoxic treatment currently would be clearly indicated in most of these patients. It appears that usually in CML-CP patients, the need for transfusion in particular of platelet is significantly lower than here observed. However, currently it also cannot be excluded that the findings be explained sufficiently by other effects and reflect the higher exposure and/or longer duration of Omacetaxine exposure in this population. Nevertheless in conclusion, it has to be ruled out that CML-CP receive too early a high cumulative myelotoxicity, which at the end might limit the prognosis and overall survival time.

We agree with the applicant that myelosuppression and associated complications were considered expected events during leukaemia therapy and can also be associated with treatment success (marrow emptying of leukaemic cells). However, in return it would be also misleading to interpret haematotoxicity observed in general as a treatment success. A CHR due to aplasia as a consequence of

myelotoxic treatment can not be used as criteria of efficacy, in particular, if patient need transfusion treatment to be stabilised not to bleed or to die from infection. The time on durable and not transient normalisation of blood count is essential for both efficacy and safety assessment. It is well known that cytoreduction alone is not a sufficient endpoint in CML.

In conclusion, without an adequate assessment of time-course of the observed TEAEs and AES in blood and lymphatic not definitive relationship to Omacetaxine treatment can be stated.

Deaths:

The sponsor reported all deaths, which occurred prior to the data cutoff date of 06 March 2009. Information on death during follow up seems to be limited in general to a period of 30 days after last contact.

Safety group 1

34 of 212 (16%) patients died as of the data cutoff date (06 March 2009). In the sponsor's opinion, the underlying disease or its complications were likely the cause of death in almost all patients (29 of 34, 85.3%) who died.

Safety group 2 (CML-202 and CML-203)

22 of 131 (16,7 %) patients died as of the cutoff date (06 March 2009). In the sponsor's opinion the underlying disease or its complications were likely the cause of death in almost all patients (18 of 22, 81.3%) who died.

Study CML-202:

16 of 66 (24,2 %) patients died as of the cutoff date (06 March 2009). In the sponsor's opinion the underlying disease or its complications were likely the cause of death in almost all patients (13 of 16, 81.8%) who died.

Due to the insufficient follow-up without information after study discontinuation, mortality as presented may be underestimated (e.g. a patient discontinued the study with ongoing grade 4 aplasia – no follow up after study discontinuation available).

A death rate of 12.5% among patients in chronic phase patients in the pivotal study, however, is already considered as unexpectedly high.

The discrepancy between number of cycles and duration of exposure is also indicative of cumulative toxicity with prior cycles requiring long delays.

The classification of relatedness of the sponsor cannot be followed in all occasions. Based on the sparse data provided in the narratives, a contribution of the myelosuppressive agent Omacetaxine and clinical complications of myelosuppression (hemorrhage, infection, bone marrow necrosis) or other complications of treatment with Omacetaxine (hyperglycemia, tumour lysis syndrome without prophylaxis) cannot be ruled out in at least 10 from 22 patients. This further confirms our concerns with regard to Omacetaxine's toxicity.

In particular, 4 of the 5 deaths observed in the CML-CP target population endorse major concerns, whether the product's hematotoxicity can be adequately handled in the target population applied.

Furthermore, as until cutoff date no deaths were reported for the CML-CP population of study CML-203, it can not be excluded that this result might indicate a lower tolerance of the target population of CML-CP patients with the T315I mutation regarding with regard to Omacetaxine's hematotoxicity.

These concerns are further substantiated by the fact that 2 of the CML-CP patients died during or after the first treatment cycle (one from bone marrow necrosis/ one from cerebral haemorrhage, both assessed as unrelated according the applicant) and pancytopenia after the first cycle associated with death was also observed in one other patient with CML-AP. This patient died 13 days after last dose of the first cycle from pancytopenia.

As indicated by the overall median of 2 cycles for patients died in this population, death occurs early in study. It is acknowledged that the prognosis of patients with CML-BP is very limited. Insofar the rate of deaths [7/11 (63%)] during cycle 1 to 3 is difficult to interpret. However, it seems to endorse our concerns that in the more advanced stage of CML-AP the highest rate of deaths was observed: 4 out of 6 (65%) deaths occurred in this population during the first three cycles. Usually a better prognosis is reported in this disease stage.

Other SAEs of special interest are bleedings and cardiac events: No SAE due to hepatotoxicity was observed. Bleeding events are only reported for the preferred term epistaxis and might be underreported. Obviously these grade 2 and lower events raise no concerns but nearly all were observed during the initial phase of treatment and might indicate the early risk. Regarding cardiac events results from non-clinical studies (hERG-channels) and ECG monitoring during the clinical studies do not suggest a potential for disruptions in electrical conductivity leading to QT prolongation at clinically relevant concentrations of OMA. Overall 6 cardiac-related SAEs (hypotension, acute coronary syndrome, congestive cardiac failure, extrasystoles and arrhythmias) were observed in safety group 2 (4 in CML-202 and 2 in CML-203). Three of these events were judged as (probably) related to OMA treatment as induced by severe anaemia.

Laboratory findings

The following laboratory parameters were evaluated according the study protocol of CML-202:

Creatinine, Urea or BUN, Uric Acid, ALT, AST, Alkaline phosphatase, Albumin, Total bilirubin, Blood glucose, WBC, Hemoglobin, Platelet Count, Neutrophils

The applicant stated that no laboratory abnormalities were reported as adverse events and no established patterns identified among these abnormal values. A sufficient summary and discussion of the findings is missed, however.

Omacetaxine has a myelosuppressive effect which predominantly occurs as thrombocytopenia and occurs more so in CML-CP patients compared with advanced disease (CML-AP and CML-BP). The myelosuppressive effects of omacetaxine can be described by the reductions in three blood cell parameters: ANC, haemoglobin, and platelet count. Nadir values ($ANC < 0.5 \times 10^9/L$, hemoglobin < 80 g/L, and platelet count $< 10.0 \times 10^9/L$) are typically reached within two to three weeks after the first omacetaxine dose administered in each cycle, and that recovery of these peripheral counts generally occurs within 1 to 3 weeks of the nadir. However, the nadir values and variability observed are not available for further assessment.

Hepatotoxicity was reported from non-clinical and earlier clinical studies. In the submission, only data for ALT and Bilirubin evaluation are included. Laboratory findings with regard to AST and Alkaline Phosphatase as well as albumin are missed, although they should be available in accordance with the study plan.

Hyperglycemia and diabetes resulting from Omacetaxine treatment are well documented in the literature and are explained by insulin resistance in literature. In the safety population group 2, 10 patients seemed to have at least one hyperglycaemic event at a maximum of grade 3. It should be noted that in one CML-CP patient, it seems from the narrative that deaths occurred shortly after first diagnosis of OMA related hyperglycemia.

Unfortunately, measurement of Creatinine Kinase (CK) was not included in clinical chemistry investigation, which would have been very helpful in excluding such events. Specific reasons why this parameter was not included in the chemistry laboratory parameter are not commented on.

Safety in special populations

In general, the applicant states that age and gender subgroup analyses were performed for the two CML studies (Studies CML-202 and CML-203), however no discernable or notable differences or trends were identified. The identification of a difference between subgroups was limited by the small sample size of the safety database. Children were not exposed with OMA.

Omacetaxine (OMA, Homoharringtonine) is highly fetotoxic in mice and based on the mechanism of action a teratogenic effect of omacetaxine is likely.

Immunological events

No statement or information concerning immunological events is available. No information about antibody formation is available in this application or in the scientific literature.

Safety related to drug-drug interactions and other interactions

The ability of omacetaxine and its primary metabolite, 4'-DMHHT, to inhibit (reversibly or irreversibly) or induce cytochrome P450 isoforms was assessed only in human liver tissue in order to identify the potential likelihood for drug-drug interactions. No clinical pharmacology studies were performed addressing drug-drug interaction.

The most frequently reported concomitant medications (i.e., those with an incidence of $\geq 20\%$ in the combined CML-202/CML-203 population in safety group 2) were:

63,4 % blood and related products (including platelets) (63.4%),

49,6% hydroxyurea,

42,7% allopurinol,

32,8% paracetamol,

32,8% fluoroquinolones,

24,4 % furosemide,

22,1% proton pump inhibitors.

Discontinuation due to AES

No systematic analysis or discussion concerning this item was presented by the applicant. The TEAEs that led to study discontinuation in more than one patient concern all hematotoxicity respectively associated complications or disease progression.

Discussion on clinical safety

It is regarded a critical short-coming of the dossier, that results from the pooled safety populations are not compared or discussed in the context for the safety observations from the pivotal trial. Instead of increasing the safety base for the application in order to learn more about less common side effects, increasing the number of patients in both described safety populations rather dilutes important safety aspects of the medical agent which are observed in the pivotal trial.

Study group 1 is disproportionally large and since a high number of patients received omacetaxine for notably shorter duration and at much lower doses that are recommended in the proposed SPC, the effect of this study population is to decrease the overall number of adverse events.

Study group 2, in which safety is analysed per disease phase, the high early mortality among patients in chronic phase is diluted since no chronic phase patients died in the supportive trial. A discussion of the impact of the considerable difference with respect to exposure and follow-up was not found.

Extrapolation from studies using lower doses per cycle are not considered relevant for the applied indication, so that study group 1 should not be discussed further. In view of the assessor, the pivotal trial and the supportive trial are regarded as adequate reference for the recommended posology. Only the pivotal trial, however, is regarded as adequate source for safety information for the applied indication, since it cannot be excluded that the molecular selection of the study population impacts on clinical

safety. Both frequency and severity of adverse events differ notably between submitted trials. Overall, data of the pivotal trial is most mature in spite of 55% of patients in chronic phase are still ongoing.

Overall, data as provided by the applicant do not appear to adequately reflect the clinical situation: Exposure data are summarised in medians or means which are inadequate in view of the high variability observed. The applicant does not discuss the strong decrease in the number of patients over the entire treatment phase. Dose delays are not discussed in the context of the high number of patients for whom information for only the first cycle is available either due to discontinuation or administrative censoring (18% in the pivotal). Dose reductions are not addressed at all. The deviation from the recommended posology in the SPC is also not discussed. In view of the high intra-individual variability and the manageable number of patients, the applicant should consider the presentation of data by individual time courses or scatter-plots.

A more critical discussion of safety data is required. Omacetaxine is intended for self-administration by patients in an out-patient setting. Observations for repeated and prolonged dose delays due to severe myelosuppression may be indicated of cumulative toxicity or slow recovery from toxicity. In view of the high intra-individual variability, toxicity appears unforeseeable and biweekly monitoring schedules as proposed by the SPC pose an important safety concern.

With regard to the TEAEs, SAEs and death observed in the pivotal study CML-202 as expected already from the non-clinical findings and earlier clinical studies myelotoxicity is the main safety in the target population. Non-haematologic toxicity seems to be manageable and low although presently, underreporting of adverse events is presumed. Overall, this is a preliminary statement and again further analysis has to be performed on more mature data. Unfortunately, no quality of life data are available from the clinical trials, which again make the weighting of such a potential advantage more difficult, in particular in an open uncontrolled study.

Very overall high rates for TEAEs (72.7%) and high rates of SAEs (73%) nearly exclusive in the blood and lymphatic system were observed, but the applicants' classification of relationship is not conclusive and cannot be assessed. However, early death after myelotoxic treatment as a consequence of SAEs in the blood and lymphatic system seems to be overall more suggestive for hematotoxicity than for disease immanent factors, also in a haematological malignancy like CML. This has to be presumed in particular, if justifications given regarding the relationship are implausible in 10 of 22 patients who died. This point of view is further substantiated by the relative high need for blood and particular platelet transfusions in CML-CP patients to bridge the myelotoxic effects of treatment shortly occurring after treatment.

At this preliminary stage of assessment, an unacceptable high hematotoxicity of Omacetaxine can not be excluded. This would preclude a sufficient safe use of this product in the target population, in particular in CML-CP patients.

Further risk and major safety concerns result from the posology, which in fact was not applied in the conduct of the pivotal study, mainly due to the observed myelotoxicity. Insofar, the proposed recommendations in the SPC for treatment and monitoring seem to be not substantiated by the pivotal study conduct and thus not acceptable. Currently, it is unclear, how any other posology could be derived and justified from the pivotal study CML-202. Treatment was extremely individualised, but even so associated with very high risks for complications probably from toxicity, in particular during the initial treatment cycles.

Another major concern results from the administration in outpatients. In this setting monitoring of patients is significantly reduced in comparison to those treated in clinics. Delays in realising treatment complications and delayed treatment of myelotoxic complications are inevitable and might have been causal in some of the deaths observed.

E.g. in a worst case scenario a CML-CP patient might have been seen by his doctor on day 7 with normalised blood counts. No further monitoring is foreseen until day 14. However, it was not realised that normalisation was transient symptom of a complete aplasia. In this case it is highly likely that the patient will further administer Omacetaxine for another week (!) and receive significant more toxicity. A period of severe and delayed aplasia may follow, which in the best case could be managed with transfusions and antibiotics until full recovery for next treatment. However, there would be a high risk to die from pancytopenia or bone marrow failure as consequence of this treatment. With the used posology several deaths have been described, in which such causality can not be excluded or presumed from the preliminary narratives. Nevertheless, only assessment of the precise data will allow rejecting such causalities.

Furthermore this product is intended in a probably growing population of patients. However, T315I patients are still a subpopulation of an orphan disease population. As the pivotal study indicates, even if this treatment is handled by specialised haematologists with an expertise in CML treatment, only very few of these specialists have treated more than one or two patients. This means that it is highly unlikely that patients from the target population will be treated from a doctor who has significant clinical experience with this the handling of the drug's toxicity. Although this situation might be managed by training and significantly increased monitoring, from the current stage even this is uncertain, in particular if patient is treated as outpatient.

In conclusion, it is not clear whether myelotoxicity is manageable in the target population with the pivotal posology even by specialised haematologists. And it must be ruled out that in particular CML-CP will receive too early a too high cumulative myelotoxicity, which at the end might limit the prognosis and overall survival time.

Cardiac events , bleedings and hepatotoxicity were identified as other SAEs of interest, but overall no alarming signals were identified during assessing of the data.

The sparse laboratory parameters were evaluated during of CML-202 (Creatinine, Urea or BUN, Uric Acid , ALT, AST, Alkaline phosphatase ,Albumin , Total bilirubin , Blood glucose, WBC, Hemoglobin , Platelet Count , Neutrophils) However, AST, AP and Albumin values were missed.

Overall hepatotoxicity and Hyperglycaemia seems to be manageable, although details given are insufficient and need further evaluation. Whether an observed increase of creatinine value during long-term treatment is relevant in the context of an observed death out of chronic renal failure in the study has to be clarified. Furthermore a death with lethal uric acid values due a case of tumor lysis syndrome

Indicate that prophylaxis of Allopurinol should be obligate in the application.

The applicant stated that no laboratory abnormalities were reported as adverse events and no established patterns identified among these abnormal values. A sufficient summary and discussion of the findings is missed, as well as a clear report on the missed value item for laboratory parameters during study conduct.

No information on safety in special populations is possible due to the limited study population in the clinical trials. The same is true with regard to drug-drug interactions, which mainly base on the in-vitro evaluation of CYP interaction. Overall no clear drug –drug interaction was identified currently.

No statement or information concerning immunological events is available. No information about antibody formation is available in this application or in the scientific literature. Skin reaction mentioned in the TEAE section will be evaluated with regard to potential allergic reactions, however, no relevant concern identified from assessment. As Tekinex is not approved worldwide, no post-marketing experience is available, with the exception of OMA/ Homoharringtonine plant formulations approved in China.

Conclusions on clinical safety

The specific limitations and feasibility problems of this application in an orphan disease are well acknowledged and considered during the assessment. However, also in this setting a clear identification of all relevant safety risk and definitive assessment has to be performed if possible.

This is currently impossible, as the data seemed to be premature and information essential for safety assessment was missed in the documentation respectively essential analyses were not performed by the applicant. Therefore, this assessment has to be preliminary until this data is available and clarification of unresolved safety issues could be performed.

The question about the meaning of the observed high myelotoxicity respectively haematotoxicity is the main safety issue of this application. Clarification is based on a clear as possible differentiation between Omacetaxine's hematotoxicity and disease-related effects on haematopoiesis. Currently, too sparse and too imprecise information is found in the submitted documents to differentiate adequately between disease related and treatment-related myelotoxic events TEAEs. The summarised statements are not sufficient to check the applicant's conclusions concerning plausibility and consistence. Information on the precise time-course of the haematotoxic events in relation to the treatment administered is a prerequisite.

In conclusion, early death after myelotoxic treatment as a consequence of SAEs in the blood and lymphatic system seems to be overall more suggestive for hematotoxicity than for disease immanent factors. This is true also in a haematological malignancy like CML, in particular if information to assess the relationship is sparse and implausible. This point of view seems to be further substantiated by the dominance of myelotoxic SAEs and the relative high need for blood and particular platelet transfusions to bridge the myelotoxic effects of treatment shortly after treatment. Thus, at this preliminary stage of assessment, an unacceptable high hematotoxicity of Omacetaxine at least cannot be excluded and is a major safety concern. It would preclude a sufficiently safe use of this product in the target population, in particular in CML-CP patients. It must be ruled out that in particular CML-CP are confronted with a risky treatment and receive too early a too high cumulative myelotoxicity, which at the end might limit their prognosis and overall survival time.

Further risk and major safety concerns result from the posology, which in fact was not applied in the conduct of the pivotal study, mainly due to the observed myelotoxicity. Insofar, the proposed recommendations in the SPC for treatment and monitoring seem to be not substantiated by the pivotal study conduct and thus not acceptable. Currently, it is unclear, how any other posology could be derived and justified from the pivotal study CML-202. Treatment was extremely individualised, but even so associated with very high risks for complications probably from toxicity, in particular during the initial treatment cycles. This seems to indicate significant problems in handling of haematotoxicity in outpatients in the current posology, in particular, as treatment in the studies was performed by haematologists with special experience in CML treatment.

A high tolerance of risks may be acceptable in patients with a life-threatening disease and a high medical need for treatment. However, risks have to be balanced by a clear, unequivocal clinical relevant benefit to come to positive overall relation. Currently the quality of data reporting and the absence of sufficient analyses of important findings is hindering the assessment of safety as well as of efficacy significantly. It is on the applicant's side to provide the clarification requested and to demonstrate that the benefit-risk relation is positive.

Pharmacovigilance system

Description of Pharmacovigilance System

Details have been provided of the Stragen Group pharmacovigilance system (Version 7 dated 16 February 2009). A statement signed by Stragen and the Stragen qualified person for pharmacovigilance, indicating that Stragen has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant has the following deficiencies:

- The description of the organisation should include an organisation chart clearly showing the position of the QPPV within the company and main reporting lines to management. Explanations on the contact with the MAH=ChemGenex shall be included. A flow chart illustrating the flow of safety reports with enough detail on the important steps (function performing the step, timelines involved) should also be provided. The diagram in appendix 7 includes elements of both above-mentioned diagrams but does not fulfil all the requirements.
- The applicant should confirm that there are written procedures covering the topics "monitoring and signal detection", "Meeting commitments to Competent Authorities in relation to a marketing authorisation", and "Management and use of databases". If the activity is covered by SOPs the description in the section on procedures should be updated accordingly, if not covered a time plan should be provided by when the SOP is expected to have been implemented. This should be before the product is placed on the market.
- Regardless the type of system used for collection, tracking, processing of safety information the indication of the responsibility for the safe operation, maintenance and validation status should be included in the DDPS.
- Major subcontracting arrangements for the conduct of Pharmacovigilance activities shall be described. The company's co-licensing and co-marketing arrangements in the EEA and identification of major responsibilities should be given. If co-licensing, co-marketing and subcontracting activities are product-specific, these have to be summarized in a product-specific addendum. The relationship/pharmacovigilance agreements in place between the applicant ChemGenex Europe SAS and the Stragen Group should be summarised to explain and justify the submission of the Stragen Group DDPS in an application for marketing authorisation by ChemGenex Europe SAS.
- A brief description of training provided to the Pharmacovigilance and non-Pharmacovigilance staff shall be given. The department/unit/ vendor etc. responsible for the Pharmacovigilance training should be identified.
- The archiving locations (both locally and centrally) of the paper pharmacovigilance source documents should be briefly described (Access control? Fire safety?).
- The applicant is requested to provide a revised description of the pharmacovigilance system answering the above-mentioned questions.

Provided that the deficiency is rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management plan

The Risk Management Plan (see summary table below) describes the identified and potential risks and other safety concerns such as missing information. In most parts the Risk management Plan follows the template and Guidelines.

Established methods for routine risk minimisation are currently in place at ChemGenex Europe S.A.S for omacetaxine via the proposed SPC and PIL. The proposals for the current and future risk management of Tekinex are in most cases agreed to. The RMP has to be updated with statements on important identified and missing information.

For the safety concern 'Potential for medication errors related to self-administration', additional risk minimization measures were proposed, in form of educational material.

However, there are some issues that need to be addressed in more detail as specified in the List of Questions.

SUMMARY OF THE EU RISK MANAGEMENT PLAN

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimisation activities (routine and additional) |
|--|---|--|
| Safety concern 1 Myelosuppression | Routine pharmacovigilance | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Section 4.2 for the management of this safety concern - Special warning in section 4.4 - Description of the undesirable effect in section 4.8 PIL: <ul style="list-style-type: none"> - Description in section 4-Possible side effects |
| Safety concern 2 Gastrointestinal disorders | Routine pharmacovigilance | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Description of the undesirable effect in section 4.8 PIL: Description in section 4-Possible side effects |
| Safety concern 3 Potential risk for cardiac disorders | Routine pharmacovigilance with close monitoring to be specifically reported in regular PSUR | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Section 4.3: TEKINEX is contraindicated in patients with NYHA class III or IV heart disease including active ischaemia or any other uncontrolled cardiac condition such as angina pectoris, cardiac arrhythmia, hypertension, or congestive heart failure - Section 4.8: cardiac disorders are listed in the summary table of adverse reactions reported in clinical trials, with the corresponding frequencies of occurrence PIL: <ul style="list-style-type: none"> - Section 2: Do not use Tekinex if you have an uncontrolled cardiac disease |

| | | |
|---|---|--|
| Safety concern 4 Hyperglycaemia | Routine pharmacovigilance with close monitoring to be specifically reported in regular PSUR. | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Section 4.4: Special warning on the monitoring of laboratory tests: Close blood glucose monitoring should be conducted in patients with glucose intolerance/type 1 or type 2 diabetes mellitus - Section 4.8: hyperglycaemia is listed in the summary table of adverse reactions reported in clinical trials, with the corresponding frequency of occurrence PIL: <ul style="list-style-type: none"> - Section 2: Take special care with Tekinex if you have diabetes or glucose intolerance, a closer monitoring of your blood glucose level may be needed |
| Safety concern 5 Missing information for patients with renal or hepatic impairment | Routine pharmacovigilance | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Section 4.4 - Special warning: TEKINEX has not been studied in patients with hepatic or renal dysfunction. Its use in such patients should be undertaken with caution |
| Safety concern 6 Missing information for patients with cardiac impairment | Routine Pharmacovigilance | Routine risk minimisation activities SPC: <ul style="list-style-type: none"> - Section 4.3: TEKINEX is contraindicated in patients with NYHA class III or IV heart disease including active ischaemia or any other uncontrolled cardiac condition such as angina pectoris, cardiac arrhythmia, hypertension, or congestive heart failure PIL: <ul style="list-style-type: none"> - Section 2: Do not use Tekinex if you have an uncontrolled cardiac disease |
| Safety concern 7 Potential for medication errors related to self-administration | Routine pharmacovigilance will include collection of information on whether a patient, caregiver, or HCP administered the drug to assess the effectiveness of the training and communication plan. For the first 3 years post MA, the regular PSURs will include an analysis of the collected information, and of the corrective | A Medication Guide will be dispensed with each prescription of Tekinex. The medication guide is provided as Section 3 of the package insert. A communication plan to healthcare professionals (HCPs). HCPs targeted in this communication plan will be oncologists, visiting nurses, and other registered HCPs. This will include: |

4. ORPHAN MEDICINAL PRODUCTS

According to the conclusion of the COMP the prevalence of CML occurs with an incidence of 1 - 2 cases per 100,000 population.

In September 2nd 2004, omacetaxine mepesuccinate received the orphan status in the treatment of chronic myeloid leukaemia with the orphan designation number EU/3/04/224.

5. BENEFIT RISK ASSESSMENT

The assessment of efficacy for both major trials (CML-202 and CML-203) is regarded as premature at the current time, since a high number of inconsistencies have first to be clarified by the applicant. Results need to be critically discussed in the clinical context of a disease in which criteria for beneficial response, drug-induced toxicity and disease progression are partially overlapping.

Introduction

Omacetaxine is a semisynthetic version of homoharringtonin, a plant alkaloid. The late-line indication sought is a molecular subset of an orphan indication "TEKINEX is indicated for the treatment of adults with Philadelphia chromosome positive chronic myeloid leukaemia who have the Bcr-Abl T315I kinase domain mutation and who are resistant to prior imatinib therapy."

CML in chronic phase in general is initially indolent. Eventually it progresses to accelerated phase and blast crisis which confers, especially in blast crisis, a poor prognosis. Treatments before the « tyrosine kinase era » constituted of interferon and of different types of chemotherapy (hydroxyurea, anthracyclins, cytarabine, amsacrin or etoposide). Highly cytotoxic treatment is usually put off until more advanced phases of the disease in order to spare patients associated toxicity. Allogeneic haematopoietic stem cell transplantation is the only curative option, but usually limited to a subgroup of selected patients in view of age restrictions or donor availability.

Tyrosine kinase inhibitors (TKIs), with imatinib firstly approved, constitute the treatment of choice and have markedly changed the course of the disease. However in about 20-30% of the patients intolerance/resistance is developed. There are different mechanisms of resistance to tyrosine kinase inhibitors with point mutations in the Bcr-Abl domain as the most common. The T315I mutation confers resistance to all the approved tyrosine kinase inhibitors and there are currently no approved treatments in patients with this mutation. The CML population who are not responding to tyrosine kinase inhibitors, especially in accelerated and blast crisis, has a poor outcome and there is a need for new therapies. Omacetaxine as unspecific protein-synthesis inhibitor is independent of Bcr-Abl binding for activity and is hence independent of mutational status of Bcr-Abl.

Dasatinib and nilotinib were approved for treatment after imatinib resistant/intolerance based on single arm studies. Complete haematologic responses (CHR) were seen for dasatinib in 87%, 64% and 26% respectively in chronic, accelerated and blast phase. Major cytogenetic responses (MCyR) were seen in 55%, 40% and 34% respectively. For nilotinib corresponding numbers for chronic and accelerated phase are 64% and 25% and 49% and 27 %.

The pivotal study, CML-202, was a single-arm study in 66 patients. Fully acknowledging that the target population is very small, this nevertheless means that only major treatment effects are possible to appreciate. For inclusion, all patients should have the T315I mutation and been treated with tyrosine kinase inhibitors, at least imatinib. The majority of patients had been treated with 2 or 3 tyrosine kinase inhibitors. In total 40 patients were in chronic phase, 16 patients in accelerated phase and 10 patients in blast phase. The very low number of patients in non-chronic phases further restricts the possibility to make a reasonable assessment of activity and even more so patient benefit.

Chronic phase: Eight of the forty patients were in CHR at study start. In total 34 (85%) of the chronic phase patients achieved a CHR with a median duration of 7.7 months. Whether this deviates favourably or not from what would be achievable in this population with a none TKI treatment alone is unclear. Major cytogenetic responses were observed in six of the chronic phase patients and complete cytogenetic responses in four. The responses occurred early with haematologic responses in cycle 1-2 and cytogenetic responses in cycle 3-4, as would be expected with cytotoxic therapy.

There were 4 deaths in patients not achieving CHR and one death in a responding patient. Median overall survival could not be estimated due to too few deaths and "survival" does not provide evidence of efficacy.

Accelerated phase: Five out of 16 patients achieved CHR with a median duration of 3.2 months and there was one complete cytogenetic response. The median time to progression was about 3 months and median survival about 1½ year. Four patients died. The seemingly very poor outcome with respect time to progression and the low cytogenetic response rate are hardly compatible with patient benefit.

Blast phase: CHR was reached in 3/10 patients, the median duration was 2.2 months and there were no documented cytogenetic responses. The median time to progression was described as 1.2 months and survival 1.8 months based on seven deaths. This outcome is considered very poor and appears even worse than what is achievable with conventional AML- induction therapy.

The supportive study, CML-203, which also is a single arm study, similar to CML-202 without the restriction to the population with T315I mutations, included 65 patients. In total 30 patients were in chronic phase, 20 patients in accelerated phase and 15 patients in blast phase. The results from the studies were similar.

Chronic phase: Similar percentage of complete haematologic responses but of shorter duration (4.7 months). The frequency of major cytogenetic responses was similar to CML-202.

Accelerated phase: Complete haematologic responses were seen in 12 (60%) with a duration of 2.5 months. One patient achieved MCyR. Median overall survival could not be estimated due to too few deaths.

Blast phase: CHR was observed in 6/15 patients. The median duration was 2.8 months. No MCyR was observed among patients in blast phase. The median overall survival of 14.5 months is based on four deaths, but with only one patient being still at risk.

These data are considered to provide some supportive evidence of activity, including evidence of poor activity in non-chronic phase patients.

Benefits /Beneficial effects

The most clinically meaningful endpoints which are realistic to be demonstrated differ by disease phase. In the more manageable chronic phase (CP), treatment aims at inducing durable cytogenetic responses which correlate with survival. Control of blood counts alone, by e.g. hydroxyurea, is not associated with improved survival. For the more advanced phases of disease (accelerated or blast phase AP or BP, respectively) prolongation of survival is the most important endpoint. In practice, both achievable rate and depth of response decrease with more advanced disease and with longer pre-treatment history.

Omacetaxine as cytotoxic agent is expected to induce both haematologic and cytogenetic responses. In order to be of clinical interest, these responses should be durable and associated with an acceptable safety profile. In the heavily pre-treated patients with all phases of CML included in the pivotal trial, it mainly induced haematologic responses and only few cytogenetic responses. Haematologic response rate among patients in accelerated or blast phase were considerably lower compared to the rate among chronic phase patients with even fewer cytogenetic responses.

Uncertainty in the knowledge about the beneficial effects

Results as currently presented by the applicant (with inconsistencies or contradictions with respect to baseline status, response assessment, follow up; see list of examples in efficacy chapter) do not allow firm conclusion with respect to clinical meaningfulness. The achievement of the primary efficacy endpoint apparently allowed for severe concomitant toxicity (thrombocytopenia or myelosuppression; see list of examples in efficacy chapter) so that the observed responses do not directly translate into clinical benefit. The observed level of concomitant toxicity is expected to impact quality of life considerably.

All haematologic responses were confirmed in the pivotal study, however, 2/7 of the cytogenetic responses were not confirmed. This is compatible with a very short duration of cytogenetic response. Here, cytogenetic responses at 6 or 12 months would be a valuable measure of efficacy. Such data, however, have not been submitted.

The median time to progression was nearly one year, but it is not clear from the study protocol how "progression" was defined in the chronic phase (nor in accelerated or blast phase).

In addition, follow up for overall survival is considered critically insufficient since it ended with discontinuation from the study and even recovery from severe adverse events was not followed up. A detrimental effect on survival has, however, to be excluded.

Data from the pivotal trial are also considered as immature for patients in chronic phase since more than half of the patients are still ongoing. An updated analysis of both the pivotal and supportive trial is required.

The apparent difference in overall survival, especially in blast phase but also accelerated phase, between the population with T315I mutations in study CML-202 and the tyrosine kinase intolerant/resistant population (mainly) without this mutation in CML-203 is of concern, if not explained by transplantations.

Further uncertainties related to the mutational status of included patients. All patients had T315I mutations confirmed either locally or centrally. However, in about 1/3 of the patients the central confirmation was negative or not performed, for different reasons. If the prognosis in relation to other treatment options than TKIs, including omacetaxine, is worse in patients with the T315I mutation, this could contribute to an overestimation of the treatment effect.

Overall benefits by subgroups

In view of the low sample size, no conclusions can be drawn for established subgroups according to age or gender. A small subgroup of currently uncharacterised patients, appear to tolerate omacetaxine much better compared to the average and may derive clinically relevant benefit from treatment.

Relative efficacy

In view of the molecular selection of patients with an orphan indication, all submitted data are uncontrolled. The patient population which has been investigated is small and highly heterogeneous. There are very limited data on haematologic, cytogenetic responses and survival in a group with T315I mutation, let alone in patient with the T315I mutation and a similar pre-treatment history, from other studies. This increases the uncertainty in the evaluation of the efficacy data. In addition, a pharmacodynamic rationale for a differential toxicity against leukaemic cells compared to normal blood cells appears to be lacking entirely.

In the context of "use of historical controls" it is stated in the current anti-cancer guideline "Dramatic effects are uncommonly documented in the treatment of malignancies, but it is acknowledged that such effects, obvious to any qualified observer, are seen occasionally". These prerequisites were fulfilled when second line TKIs were approved, but are not fulfilled by this application.

Conclusion with respect to beneficial effects:

No firm conclusion can be drawn at the present time.

Risks/Unfavourable effects

Omacetaxine is a potent myelosuppressive agent. The posology as recommended per study protocol (and in the SPC) had not been implemented in the clinical trials in which it was aimed at maintaining a 28 day cycle instead of administering the recommended dosing. Excessive hematotoxicity including early deaths and prolonged dose delays were observed, especially following early cycles with 14 dosing days. Very high intra-individual variability with respect to tolerability had been described for omacetaxine (Marin 2005). The dose-finding study referred to by the applicant even concluded that new dose-finding studies are required in view of the high toxicity. Overall, the agent appears to be associated with unforeseeable toxicity with lengthy recovery in a considerable proportion of patients. A poorly conceived dose-finding including an unclear monitoring schedule and the seemingly unforeseeable severity of toxicity is considered a critical risk since omacetaxine is intended for home use, i.e. self-administration by the patient in the absence of medically trained personnel. In contrast to these observations, the applicant concludes good tolerability of omacetaxine and does not address the large intra-individual variability.

Quality: Tekinex is intended for self-administration at home. There are no data to show the suitability of the syringe for its intended use, i.e. the capability of the syringe to withdraw different volumes of the reconstituted product, and that a risk for dosing error is minimised.

Toxicology: Omacetaxine doses under 1 mg/kg/d results in lethality in mouse, rabbit and dog. Omacetaxine has a narrow safety margin characterised by a steep dose-response curve with very close NOAEL and LD doses. The NOAEL in the mouse was below the lowest tested dose and the NOAEL in the dog was equivalent to the lowest tested dose, which is several fold lower than the clinical dose, so a safety margin between animal doses (or exposure) and human dose (or exposure) cannot be estimated. There are strong species differences, suggestive of important metabolic differences.

Pharmacokinetics: The main deficiency is that the major elimination pathway has not been characterised and thereby potential risk at organ impairment or drug-drug interactions cannot be adequately estimated. This uncertainty might, however, to some degree be handled by SPC warnings.

Clinical: The adverse events observed are mainly haematologic with thrombocytopenia, anemia and neutropenia as the most common events, but less than 10% of the patient had infections or bleedings.

Gastrointestinal side effects, such as diarrhoea and nausea, were seen in about 40% and 30% of the patients. Asthenia/fatigue and pyrexia were also common, as well as injection site disorders and skin related toxicity.

About 80% of the patients had adverse events of grade 3- 4. Also here the most common events were haematologic. Serious adverse events were recorded in about 60% of the patients, there were more SAEs in blast phase as compared to accelerated and chronic phase patients, which to some extent can be expected from the disease phase per se. There were also more events leading to death in blast phase as compared to the other phases.

Uncertainty in the knowledge about the unfavourable effects

A major problem is that treatment-related toxicity to a large extent is overlapping with symptoms from the disease, especially regarding the most common adverse events. Thus, also the assessment of safety is hampered by the absence of proper control arms. The experience is also limited with regard to number of patients and duration of exposure, especially in accelerated phase and blast phase.

The analysis of treatment compliance may be anticonservatively biased since doses as in the preceding cycle were imputed in the absence of a correctly kept patient diary. Inconsistencies between number of dosing days analysed and patient narratives were detected which further highlights the resulting overestimation of doses received. In addition, based on the way of recording adverse events in the most relevant prospective trials, the frequency of adverse events may be underestimated: Patients were asked to recollect adverse events on the occasion of visits, but suggestive questioning was discouraged. Overall, an overestimation of tolerability is likely. At the present time, it is not possible to predict which patient will tolerate omacetaxine better compared to the average.

The risk of application errors and overdosing have not been sufficiently addressed by the applicant who concluded an overall good tolerability of the recommended posology. The compliance with correct disposal of this cytotoxic agent was not addressed.

Another important risk not addressed by the applicant is a possible detrimental effect of omacetaxine on the subsequent treatment course (acceleration of progression, detrimental effect on survival due to carry-over toxic effect).

A full evaluation of toxicity is further hampered by the limitations in the presentation of adverse events in the study reports, as in the compilation only the worst grade and one event per issue per patient are counted. Furthermore, comprehensive information on duration of the events and occurrence with regard to cycles is missing.

Conclusion with respect to unfavourable effects

Altogether, the risk profile is what would be expected from a cytotoxic compound. There is clearly a safety issue, however, over a drug with significant toxicities and an apparently unjustified posology which is intended for self-administration by the patient.

Balance/Importance of favourable and unfavourable effects /Benefit-risk balance

The documented activity of omacetaxine in the target population for this application is overall low. In patients in accelerated and blast phase, it is too low to be of likely benefit to the patients. In the chronic phase the activity is modest and does not outweigh toxicity and tolerability concerns.

Discussion on the benefit-risk assessment

At the present time, it is not possible to explain the observation of a small subgroup of patients who appear to tolerate omacetaxine better compared to the average. The characteristics of these patients or how they could be selected remained unclear. Efficacy of omacetaxine appears to be limited to patients in chronic phase. While a beneficial effect in patients in accelerated phase is questionable, no meaningful effect was demonstrated in patients with blast phase. Therefore, urgently needed studies to improve posology should be performed in patients with chronic phase or possibly accelerated phase. Patients with chronic phase CML, however, represent an extremely heterogeneous population and the necessity for highly cytotoxic treatment is difficult to reflect by inclusion criteria. Therefore, comparative studies using investigator's best choice as control should be performed.

5.1. Conclusions

The overall B/R of Tekinex in CML patients carrying the T315I mutated BCR-ABL gene is negative.