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Performance of the Agency's scientific procedures: Survey 2010 for medicinal products for human use

Management Board meeting 17 March 2011

Background note

This is the yearly report to the Management Board on the Performance of the Agency's scientific procedures conveying descriptive statistics on new marketing authorisation applications and extensions of indication for medicinal products with existing marketing authorisations that had an outcome in 2010 (a positive or negative opinion or a withdrawal of a marketing authorisation application).

Matters for consideration

The objective of this report is to give insights into some aspects of new marketing authorisation applications and extensions of indications for already marketed products. It should be noted that whereas this report refers to marketing authorisation applications with outcomes (include those that received a positive or negative opinion or were withdrawn), the EMA official "Annual Report", refers to the total number of applications submitted or the total number of applications with an outcome during the year. This report may also occasionally count outcomes twice namely when outcomes for the same MAA occur twice in consecutive years. This may explain why figures may differ between the official annual report and this report. The "EMA Scientific Memory database" has been the basis for these analyses. The analysis set encompasses applications with an outcome in the CHMP assessment process from 1 January 2010 until 31st December 2010. Duplicate applications, i.e. applications which rely on the same dossiers have been counted only once. For initial applications also so called "informed consent" applications have been excluded from the analysis.

Main Findings

- There was a significant fall (48%; from 64 to 33 applications) in the number of new marketing authorisation applications with an outcome in 2010 compared with 2009.
  - "New Active Substance" applications have fallen from 48 application in 2009 to 22 in 2010
- There was also a significant fall (51%; from 49 to 24 applications) in the number of new extension of indication applications with an outcome in 2009 compared with 2010.

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Review of initial applications for marketing authorisation and extensions of indications with outcomes in 2010

In 2010 there were a total of 64 new marketing authorisation applications that reached an outcome in the Committee for Medicinal Products for Human Use (CHMP) scientific evaluation. In the same time period 28 applications for extensions of indications (adding new treatment options for medicines that are already authorised in the European Union) reached an outcome in the CHMP.

In the following sections some further analyses of these new marketing authorisation applications and extensions of indications are reported. Detail is given to the benefit-risk balance as expressed by the CHMP to explain the reasoning behind the views taken by our Scientific Committee (annex).

1. Initial applications for marketing authorisation with an outcome in 2010

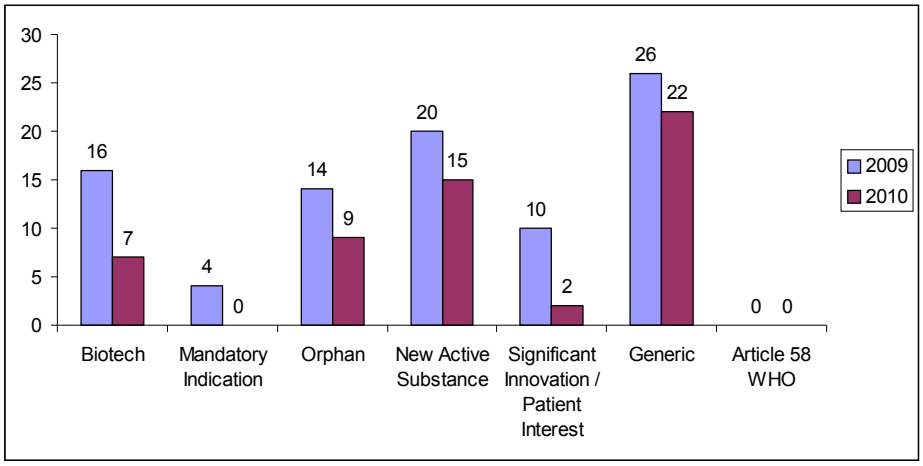
1.1. Eligibility to the centralised procedure

Eligibility criteria for 55 applications (duplicate and informed consent applications excluded) with an outcome in 2010 are described in figure 1 alongside the data reported in 2009.

Not counting the 22 generic applications, 33 applications with an outcome remain. This signifies a 48% reduction from the 64 applications with an outcome reported for 2009. For last years' report please see http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/03/WC500078395.pdf.

This significant fall in the number of new initial marketing authorisation applications with an outcome in 2010 compared with 2009 seems to affect all aspects of eligibility. There appears to be a greater "loss" of innovation in the mandatory scope as compared with the optional. There are for example no new active substances in the area of the "mandatory indications". Such a trend was also noted in last year's report.

Figure1. Eligibility criteria for applications with outcomes in 2009 and 2010.



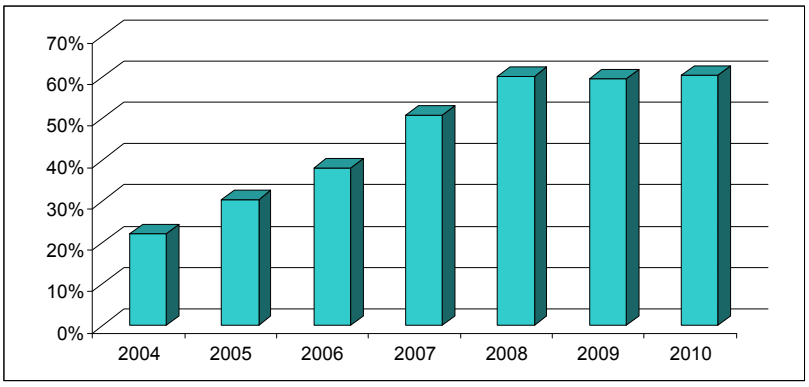
1.2. Outcome of Marketing Authorisation Applications and Scientific Advice

Twenty-four (73%) of the 33 applications reached a positive outcome in the CHMP review leaving 9 (27%) unsuccessful (negative opinion or withdrawn). Two (Cerepro and Tyvaso) of the 9 orphan medicinal products failed as did 1 (Cerepro) of the 4 (Cerepro, Esbriet, Ruconest and Orphacol) applications that were submitted by small and medium sized companies (SMEs). Cerepro was the only "advanced therapy" application in 2010.

Four applications were approved conditionally (Arzerra, Arepanrix, Humenza and Votrient). Pumarix and Orphacol were approved under exceptional circumstances. VPRIV and Pumarix were subject to accelerated assessment (150 days assessment). During the assessment of 7 applications (Cerepro, Arzerra, Votrient, Xeplion, Daxas, Fluenz, Zeftera), the CHMP convened scientific advisory groups or other expert groups prior to final recommendation. Twelve oral explanations took place where the applicant had the opportunity to clarify certain issues in front of the CHMP.

The proportion of applications with scientific advice (SA) remained rather constant between 55 to 60% over the last 3 years (Figure 2). Note that this analysis does not include the generic applications where SA is generally lower than for applications with a more comprehensive development. A recent publication (1) from the Agency sets out the importance of compliance with scientific advice for the success of the marketing authorisation application.

Figure 2. Proportion of application (excluding generics and duplicate applications) that received SA – by outcome year.



1.3. "New Active Substance"

The term New Active Substance [1] (NAS) is defined in EU pharmaceutical regulation to include novel molecules that are either chemically-synthesised or from a biological source. We modified (2) the existing definition to exclude biosimilar applications - as these were deemed not to be truly 'new' developments and when multiple product applications were filed for the same NAS, only one was

[1] - a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance
previously authorised;
- a biological substance previously authorised as a medicinal product in the European Union, but differing in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised as a medicinal product in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union.

counted. Our definition of NAS is similar but not identical to the FDA's definitions of new molecular entities and biologic licence applications.

As a result 11 (table 1) of these 33 applications were not regarded as "new active substances" leaving 22 (67%) as "NAS" for 2010 (table 2 A and B). Seventeen (77%, table 2A) of these 22 applications were recommended by the CHMP for marketing authorisation; 5 (23%, table 2B) received a negative CHMP opinion or were withdrawn before the opinion. As indicated below, this signifies a much lower failure rate compared with 2009 (40%), although the numbers are low.

Of the 17 approved NAS applications, 11 (65%) received scientific advice as did 3 of the 5 with a negative outcome. There were 3 NAS applications coming from SMEs. Five of the 17 approved NAS applications were prophylactic flu vaccines (table 2). That leaves 11 NAS for treatment and one as a diagnostic agent.

In the national decentralized procedure a total of 4 new active substances reached an outcome for each of the years 2009 and 2010.

It may be of interest to remind of what we reported in 2009, http://www.ema.europa.eu/docs/en_GB/document_library/Other/2010/03/WC500078395.pdf. We then reported 48 NAS applications with an outcome; 29 (60%) were recommended by the CHMP for marketing authorisation, 19 (40%) received a negative CHMP opinion or were withdrawn before the opinion. Of the 29 approved NAS applications, 21 (72%) requested Scientific Advice (SA) from the CHMP during the course of drug development, as did 11 (58%) of the 19 applications with a negative outcome. The proportion of small and medium-sized enterprises (SMEs) among applicants for MAAs with negative outcomes (6/19; 32%) was higher than among approved applications (4/29; 14%).

A study is currently ongoing to further clarify whether failed drug applications are the result of failed drug development or a negative benefit/risk ratio where available data indicate to the CHMP that risks appear to outweigh the possible benefits. In a previous publication from the Agency (3) in 2002, lack of adequate controlled clinical trials as identified after the first cycle of assessment (day 80) was the most important factor predicting a negative outcome.

The Annex provides the benefit-risk balance as expressed by the CHMP in the final assessment of the "NAS" applications with an outcome in 2010. The narratives are copied from the published European Assessment Reports (EPAR). Since not all EPARS are published as of to date (February 2011) not all narratives have been published in this report.

Table 1. The 11 products not regarded as "new active substances".

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
Ibuprofen-Diphenhydramine hydrochloride Wyeth	Ibuprofen /Diphenhydramine hydrochloride	Fixed dose combination originally eligible as a new active substance	Pain	Withdrawn prior to opinion
Movectro	Cladribine	Significant innovation/patient interest	Multiple Sclerosis	Negative by majority. Negative after re-examination in January 2011
Nivestim	Filgrastim	Similar biological application	Neutropenia	Positive by consensus
Orphacol	Cholic acid	Orphan medicinal product	Inborn errors in primary bile acid synthesis	Positive by consensus

Name	INN*	Eligibility	Therapeutic Area	CHMP Outcome
Ozurdex	Dexamethasone	Significant innovation/patient interest	Macular oedema	Positive by consensus
Rasival	Aliskiren hemifumarate/ valsartan	Fixed dose combination originally eligible as a new active substance	Hypertension	Withdrawn prior to opinion
Teysuno	Tegafur/gimeracil /oteracil	Orphan medicinal product	Gastric cancer	Positive by consensus
TOBI Podhaler	Tobramycin	Orphan medicinal product	Cystic fibrosis	Positive by consensus
TWYNSTA	Telmisartan /amlodipin	Fixed dose combination originally eligible as a new active substance	Hypertension	Positive by majority
Tyvaso	Trepostinil sodium	Orphan medicinal product	Pulmonary arterial hypertension	Withdrawn prior to opinion
Xeplion	Paliperidone	Automatic access	Schizophrenia	Positive by majority

* INN: International non-proprietary name

Table 2. The 22 products regarded as "new active substances"

A. Positive Outcomes (n=17)

Aflunov			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Prepandemic Influenza Vaccine (H5N1)	Biotech medicinal product.	Prepandemic influenza vaccine	Positive by consensus

Arepanrix			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Split virion inactivated AS03	New active substance	Pandemic influenza vaccine	Positive by consensus

Arzerra			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Ofatumumab	Orphan medicinal product	Chronic lymphocytic leukaemia (CLL).	Positive by consensus

Brilique			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Ticagrelor	New active substance	Acute coronary syndrome	Positive by consensus

Brinavess			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Vernakalant hydrochloride	New active substance	Atrial fibrillation	Positive by consensus

Daxas			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Roflumilast	New active substance	Chronic obstructive pulmonary disease (COPD)	Positive by majority

Esbriet			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Pirfenidone	Orphan medicinal product	Idiopathic Pulmonary Fibrosis (IPF)	Positive by consensus

FLUENZ			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Influenza vaccine (live attenuated, nasal)	Biotech Medicinal Product	Prophylaxis of seasonal Influenza	Positive by consensus

Humenza			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Pandemic Influenza Vaccine (H1N1)	New active substance	Pandemic Influenza	Positive by majority

Prolia			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Denosumab	Biotech medicinal product	Osteoporosis	Positive by consensus after revision of opinion from 2009

Pumarix			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Pandemic influenza vaccine (H5N1) Split virion, inactivated, adjuvanted.	Biotech medicinal product.	Pandemic Influenza	Positive by consensus Mock-up pandemic influenza vaccine that is approved only for use in a declared pandemic (WHO Phase 6).

Rapiscan			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Regadenoson	New active substance	Radionuclide myocardial perfusion imaging (MPI).	Positive by consensus

Ruconest			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Conestat alfa	Orphan medicinal product	Hereditary angioedema (HAE)	Positive by consensus

Sycrest			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Asenapine	New active substance	Bipolar disorder	Positive by majority

Votrient			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Pazopanib	Orphan medicinal product	Renal cell carcinoma	Positive by majority

VPRIV			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Velaglucerase alfa	Biotech medicinal product	Gaucher disease	Positive by consensus

Xiapex			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Collagenase clostridium histiolyticum	New active substance	Dupuytren's contracture	Positive by consensus

B. Negative Outcomes (n=5)

Cerepro			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Sitimagene ceradenovec – adenoviral vector-mediated Herpes Simplex Virus-Thymidine	Orphan medicinal product	Glioma	Withdrawn after appeal Note that for technical reasons Cerepro was also counted in last year's report

Comfyde			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Carisbamate	New active substance	Epilepsy	Withdrawn before the opinion

Joulferon			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**

Joulferon			
Albinterferon alfa-2b	Biotech medicinal product	Chronic Hepatitis C	Withdrawn prior to opinion

Zeftera			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Ceftobiprole medocaril	New active substance	Bacterial infection	Negative after appeal by majority

Zenhale			
INN	**Eligibility to the CP**	**Therapeutic area**	**Outcome**
Mometasone furoate Anhydrous + Formoterol Fumarate Dihydrate	Fixed dose combination originally eligible as a new active substance	Asthma	Withdrawn prior to opinion

References

1. Regnstrom J, Koenig F, Aronsson B, Reimer T, Svendsen K, Tsigkos S, Flamion B, Eichler HG, Vamvakas S. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur J Clin Pharmacol. 66,39-48 (2010)
2. Eichler H-G, Aronsson B, Abadie E, and Salmonson T. New drug approval success rate in Europe in 2009. Nat Rev Drug Discov. May;9(5):355-6 (2010).
3. Pignatti, F. Aronsson, B, Gate N, Vamvakas S, Wade G. The review of drug applications submitted to the European Medicines Evaluation Agency: frequently raised objections, and outcome. Eur. J. Clin. Pharmacol. 58, 573–580 (2002).

2. Applications for extension of indication with an outcome in 2010

In 2010, the CHMP completed the assessment of 28 applications for extensions of indications for centrally authorised products (CAPs). Four (4) of these were duplicate applications and the remaining 24 applications were thus taken into account in the various analyses. 23 out of 24 of these applications reached a positive opinion. For two procedures the positive opinion related to updates of the product information other than section 4.1 of the SPC ("therapeutic indications").

It may be of interest to remind of what we reported in 2009. Forty-nine extension of indication were analysed. Forty-four (90%) of 49 applications reached a positive CHMP opinion. For a small subset (12%), the positive opinion related to updates of the product information other than section 4.1 of the SPC ("therapeutic indications").

Similar to the pre-authorisation procedures, there is a significant (51%; from 49 to 24 applications) fall in the number of extension of indication applications with an outcome in 2010 compared with 2009. This fall is particularly noticeable in the anti-infectives and vaccines (64%) Central Nervous System and Ophthalmology (71%) and Endocrinology, Metabolism and Cardiovascular (73%) therapeutic areas.

In 2010, scientific advice was given in relation to the sought new indication for 4 of the 24 procedures (17%), which is less than in 2009 (26.5%).

SAGs were convened during the review of 4 extensions of applications procedures in 2010 (17% of procedures) in the oncology and CNS therapeutic areas which is more than in 2009 (14%).

The Annex provides the benefit-risk balance as expressed by the CHMP in the final assessment of the extensions of indication for which the Committee gave positive opinions, adding new treatment options for medicines that are already authorised in the European Union. The narratives are copied from the published European Assessment Reports (EPAR). Since not all EPARS are published as of to date (February 2011) not all narratives have been published in this report. Information is provided by therapeutic area:

ANNEX

1. Benefit Risk assessments - from the EPAR of the "new active substance applications" with positive outcomes in 2010. (As available on 07 February 2011)

Aflunov

Benefits

- Beneficial effects

The H5N1 strain is considered as a likely candidate from which pandemic influenza may evolve. In contrast to the recent influenza pandemic caused by the A/H1N1 (A/California/7/2009) strain, which seemed to be easily transmitted between humans but had a lower mortality rate, the avian origin H5N1 strains caused so far influenza outbreaks with rare human transmission but high mortality rate (63%). In case of a H5N1 pandemic, the use of a pre-pandemic vaccine, even if not perfectly matched to the pandemic virus and perhaps giving very low protection, may nevertheless prevent some infections and deaths whilst waiting for the specific pandemic vaccine.

Overall the production of a vaccine against a potential influenza viral strain during the interpandemic period may: i) permit early vaccination at the beginning of a pandemic when the "first track pandemic" vaccine is not yet available; ii) prime during pre-pandemic stages to reduce mortality against a closely matched pandemic strain in those countries were infections are occurring; iii) reduce the chance of an emergence of a reassortant pandemic strain by vaccinating those (e.g. veterinarians, poultry workers…) at high risk of both avian and human virus infection.

The production process of AFLUNOV is based on long experience with the other Applicant's influenza vaccine, the interpandemic Fluad. In addition, objections raised in the context of the Focetria MAA have been taken onto consideration in the present application. Therefore, the process is well established and raises no substantial quality concerns.

The benefit of a prepandemic vaccine is assessed primarily based on the CHMP immunogenicity criteria and the use of animal challenge data. As already established for several other vaccines, the addition of an adjuvant (regardless of the HA dose) increases the vaccine's reactogenicity. However, important advantages of including an appropriate adjuvant are immune potentiation and antigen sparing, which are especially important in pandemic situations. The vaccine was proven to induce satisfactory antibody responses in healthy adults below and above 60 years of age, with low HA antigen quantities. However, although no major concerns exist on the adequacy of a two dose schedule, it may occasionally be insufficient to complete full maturation of a developing anti H5 immune response, in particular as regards potential immunity against H5N1 variants different from the vaccine strain. Additionally, results from the only submitted paediatric study to date suggested a sufficient immune response also in the group aged 6 months-17 years (study V87P6).

In subjects primed against the H5N3 strain, a heterologous booster with AFLUNOV administered after 6 to 8 years from the priming induced high and rapid serological and cell mediated immune responses against both strains and a variety of others. Thus the strategy of pre-pandemic vaccination with an adjuvanted vaccine would allow boosting with a single dose once the actual pandemic strain is known even 6-8 years later. This suggested that immunological memory had been induced by the H5N3 vaccination series which persisted several years and that B cells can rapidly be expanded upon an adjuvanted booster vaccination containing a different pandemic strain.

Concomitant administration of AFLUNOV with a conventional subunit seasonal influenza vaccine did not negatively impact the immune response to either the pandemic H5N1 strain or to the seasonal strains.

- Uncertainty in the knowledge about the beneficial effects.

At present the benefit of AFLUNOV can only be assumed from the data on the immunological responses elicited following a primary series and a booster against the vaccine strain and against antigenically drifted strains of influenza A/H5N1 virus. SRH and MN assays were considered the most appropriate serological tests for assessing immunogenicity of AFLUNOV, as it has already been the case for Focetria H5N1. However it is not fully understood why immunogenicity results obtained by the Applicant with HI assay are not always satisfactory. In particular, the lack of consistency across pivotal studies for some results measured by HI and the suboptimal results obtained with the HI assay in the largest study V87P13 are still unexplained.

The expected benefit of AFLUNOV is to prime immunological response in fully susceptible subjects against H5N1 virus and therefore to allow shorter time to induce appropriate protection against clinically apparent infection and/or severe disease in case of an influenza pandemic due to H5N1. This is based on an assumption that vaccination with AFLUNOV containing antigens derived from A/Vietnam /1194/2004 will provide a clinically useful degree of cross-protection against a H5N1 strain causing the pandemic. Results reported for AFLUNOV/Prepandemic Influenza Vaccine H5N1 from heterologous challenge showed limited cross-reaction. For these reasons the applicant is requested to continue to evaluate cross-reactivity and cross-protection in the post-authorisation period against emerging strains considered to have some potential to cause a pandemic.

Risks

- Unfavourable effects

AFLUNOV is commonly or very commonly associated with a range of local and systemic adverse reactions but these are not often of severe intensity and the safety profile would not preclude the use of the vaccine in healthy adults aged 18-70 years. The experience of AFLUNOV in the elderly and in a population with co-morbidities is limited. No data are available in immunocompromised patients.

Although limited safety data are available for AFLUNOV in the elderly population, post-marketing experience with Fluad (containing adjuvant MF59) in elderly subjects is extensive. Overall, considering the cumulative exposure, including all age groups, the reporting frequency of all adverse events is 1.4 cases per 100,000 sold doses. The observed differences in AEs between adults and elderly subjects are consistent with what observed in clinical trials and do not seem to represent a safety risk.

Data on pregnancy outcomes are limited.

- Uncertainty in the knowledge about the unfavourable effects

The current safety database of AFLUNOV was considered to be sufficient to describe adverse reactions that occur uncommonly and to give an indication of any rare events. However, there are some adverse reactions known to be very rarely associated with influenza vaccines and it was not possible to predict if higher rates might be observed with AFLUNOV compared with, for example, seasonal influenza vaccines. Safety in elderly subjects above 70 years of age was not assessed.

As the vaccine is intended for use in a non-emergency situation, careful consideration should be given to its administration to pregnant women, for whom vaccination could be deferred till the end of pregnancy. Sporadic cases of pregnancy were reported in some studies, but the number of cases was very small and no firm conclusion could be drawn. However, safety of AFLUNOV in specifically vulnerable populations or in risk populations might be extrapolated from Focetria H1N1 which has been

widely used during the current pandemic. Final data on pregnancy outcomes with Focetria H1N1 are awaited, thus final conclusions on the safety profile of AFLUNOV during pregnancy cannot be drawn at present.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Data on the immunological responses elicited following a primary series and a booster vaccinations against the vaccine strain and against antigenically drifted strains of influenza A/H5N1 virus, supported the claim that AFLUNOV, in the interpandemic period may

i) permit early vaccination at the beginning of a pandemic when the "first track pandemic" vaccine is not yet available;

ii) prime during pre-pandemic stages to reduce mortality against a closely matched pandemic strain in those countries were infections are occurring;

iii) reduce the chance of an emergence of a reassortant pandemic strain by vaccinating those (e.g. veterinarians, poultry workers…) at high risk of both avian and human virus infection.

These benefits together with the acceptable safety profile of AFLUNOV are considered of significant clinical relevance and overcome the uncertainties due mainly to the limited experience in elderly and in subjects with co-morbidities or immunocompromised. Of note, the limited experience with AFLUNOV during pregnancy suggests as a precautionary approach to defer the administration of the vaccine.

Conclusions on benefit-risk balance

In conclusion, as with any rare, catastrophic event, it is impossible to determine the likelihood of an H5N1 pandemic. Therefore the benefit of a pre-pandemic vaccine is not easy to predict. Vaccination with pre-pandemic influenza virus vaccine (if specific) could be an effective way to reduce the threat of a possible influenza pandemic while an acceptable safety profile can be concluded from the currently available safety data base. Thus, following thorough evaluation of immunogenicity and safety data provided in the MAA the CHMP is of the opinion that a two doses regimen of AFLUNOV has a favourable benefit/risk ratio in the prophylaxis of infection by H5N1 subtype of Influenza A virus.

The overall benefit-risk balance of AFLUNOV is positive.

Risk management plan

A risk management plan including an Efficacy Follow-up Plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- in case of pandemic, pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- additional risk minimisation activities were required (as listed in paragraph 3.7).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the risk-benefit balance of AFLUNOV in the prophylaxis of infection by H5N1 subtype of Influenza A virus was favourable and therefore recommended the granting of the marketing authorisation.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed. The CHMP reviewed the already available paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Arepanrix

Benefits

The CHMP considered that the real benefits of Arepanrix can only be assessed by effectiveness studies during the pandemic as outlined in the RMP. At present the benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination with a similar vaccine, Pandemrix plus data available from administration of Arepanrix A(H1N1)v vaccine during clinical trials and post-authorisation use in Canada.

Pandemrix and Arepanrix have shown (as H5N1 vaccine) to have comparable immunogenicity in adults and in the elderly that indicate comparable responses between Dresden and Quebec manufactured vaccines.

In addition, the HI data at D21 in study H1N1-017 showed that both vaccines (as H1N1 vaccine) elicited immune responses that met the CHMP criteria in adults regardless of baseline serostatus and prior vaccination history.

There are limited data from clinical trials as yet in children with Arepanrix. An extrapolation of immunogenicity data on use of Pandemrix in children to use of Arepanrix in the same age groups might be considered on the basis of the comparable immunogenicity in adults. Therefore it is assumed based on immunogenicity considerations that the recommendations for Pandemrix H1N1v regarding use in children should also apply in principle to Arepanrix H1N1v.

Based on the data available with A(H1N1)v from clinical trials and post marketing with Arepanrix and

Pandemrix the expected benefit of Arepanrix is to provide some protection against clinically-apparent infection due to A(H1N1)v.

Risks

Limited clinical data with Arepanrix do not suggest a different safety profile than Pandemrix or the one confirmed by clinical trials with Arepanrix or Pandemrix containing vaccine constructs manufactured using both H1N1 or H5N1 antigen.

Extensive use of Arepanrix H1N1 in Canada and Pandemrix H1N1 in Europe throughout all age groups from 6 months onwards can be considered sufficient to confirm the safety profile of Arepanrix to be favourable.

Conclusion

CHMP considers that the eligibility in accordance with Article 2(2) of Council Regulation (EC) No 507/2006 together with the criteria of conditional Marketing Authorisation in accordance with and 4 of Council Regulation (EC) No 507/2006 are fulfilled.

It can be further concluded that Arepanrix provides comparable immune responses and safety profile to the approved vaccine Pandemrix. The Benefit Risk ratio is considered positive.

Recommendation

On the basis of the available data for Arepanrix the CHMP considered by consensus that the risk benefit balance of Arepanrix A(H1N1)v for the prophylaxis of influenza in an officially declared pandemic situation, in accordance with official guidance, was favourable. Therefore CHMP recommended the granting of the conditional marketing authorisation.

Arzerra

Risk-benefit assessment

Ofatumumab treatment was accompanied by a high response rate in CLL patients refractory to fludarabine and alemtuzumab treatment (58%) and a slightly lower response rate (47%) in fludarabine refractory bulky lymphadenopathy patients for whom aletuzumab therapy is considered inappropriate. At the same time, the use of ofatumumab was accompanied by serious and life-threatening complications (infections and neutropenia), which, however, are also manifestations of the underlying disease, so that the safety profile does not cause particular concern overall. Having considered the argumentation put forward by the Applicant and the recommendation of the oncology Scientific Advisory group (SAG), the CHMP concluded that the benefit-risk of ofatumumab is positive for the double (fludarabine and alemtuzumab) refractory population but not for the fludarabine refractory, bulky lymphadenopathy population. However, there is a need to further confirm the positive benefit-risk in the double refractory population through the conduct of controlled trials in CLL disease settings in which such trials are feasible (fludarabine refractory, bulky lymphadenopathy population and earlier lines of therapy). Thus, the CHMP proposed a conditional marketing authorisation, after having consulted the applicant. The CHMP considered that ofatumumab is both a medicinal product which aims at the treatment of a life-threatening disease and an orphan medicinal product, and therefore falls within the scope of Regulation (EC) No 507/2006. Moreover, the CHMP considered that ofatumumab fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

(a) Efficacy in terms of response rate was demonstrated in a pivotal and a supportive open label, single arm trials conducted in fludarabine and alemtuzumab double-efractory patients. Overall, a response rate of 58% was observed. Treatment with ofatumumab was associated with adverse events indistinguishable from the underlying disease which don't give rise to particular concern. Therefore, the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

(b) There is a need to gain more understanding about the benefit-risk profile of ofatumumab. To this end, the applicant will provide comprehensive clinical data from ongoing Phase III randomised, controlled clinical studies in earlier disease settings. In addition, it is important to further confirm the high response rate and control of the disease in the refractory setting through controlled trials and extended ofatumumab treatment. The applicant will conduct a controlled trial comparing ofatumumab against physician's choice in fludarabine refractory, bulky lymphadenopathy patients. After 24 weeks of treatment, patients on the ofatumumab arm will be further randomised to either extended ofatumumab treatment or to observation alone. Finally, the applicant will conduct a Phase IV observational study. The applicant has provided draft proposals and estimated timelines as well as assurance about the feasibility of the last two studies. The timelines of these studies will be confirmed upon submission of the final study protocols within three months of the conditional marketing authorisation date. Thus, it is likely that the applicant will be in a position to provide the comprehensive clinical data.

(c) Currently there are no approved treatment options for fludarabine and alemtzumab refractory CLL patients. Ofatumumab has shown a high response rate and this effect was clinically significant in this patient population. In accordance with the definition of Article 4, paragraph 2, of Regulation (EC) No 507/2006, the medicinal product concerned will be of major therapeutic advantage to those affected. Therefore, unmet medical needs will be fulfilled.

(d) In view of the favourable benefit-risk profile, the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Arzerra in the treatment of Chronic Lymphocytic Leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab was favourable and therefore recommended the granting of the conditional marketing authorisation.

Brilique

Benefits

- Beneficial effects

The pivotal trial, PLATO, compared ticagrelor to clopidogrel administration both on top of treatment with low dose ASA in prevention of thrombotic events in patients with ACS including patients managed medically, and those who are managed with PCI or CABG. This is considered justified as the common treatment approach in ACS is treatment with ASA and with the addition of clopidogrel. In the treatment of ACS conditions, there is a significant risk for recurrent MI or occurrence of death within 30 days after a patient is presented with ACS, particularly for STEMI ACS. An endpoint including CV death, MI and another objective endpoints is considered essential. In PLATO the combined endpoint of CV death, MI and stroke is considered appropriate, but overall death is also considered of substantial importance. The beneficial effect of ticagrelor is convincing as both a beneficial effect on the primary endpoint is demonstrated at 30 days of follow-up (HR 0.88; p=0.0446) and maintained in the longer term of up to 12 months for the primary endpoint (HR 0.84; (0.77-0.92), p=0.0003) as well as for overall death. An extensive group of patients has undergone invasive management, in particular PCI (approximately 60%). For both the overall intervention subgroup as well as for patients undergoing PCI the beneficial effect of ticagrelor is consistent with the overall beneficial effect. Of particular importance is that this was irrespective of timing of PCI (less than 24 hr versus at-any-time). Post hoc analyses showed that consistent benefit is observed, with a slight advantage for medically managed patients. The observed lower benefit for the North American subgroup is further discussed under risks above. Although more adverse events and discontinuations due to adverse events occurred with ticagrelor, there were fewer numbers of severe adverse events and deaths and sensitivity analyses did not demonstrate any differences in treatment effect based on differences in discontinuation.

- Uncertainty in the knowledge about the beneficial effects.

Although there is a beneficial effect demonstrated for MI and CV death, there seems to be a negative effect on stroke (HR 1.17 (0.91-1.52, P=0.2249). It is not known whether a beneficial effect could be demonstrated in patients with a history of previous intracranial bleed. However, as it was an exclusion criterion in the PLATO trial, history of intracranial haemorrhage has been contra-indicated in the SmPC. Further, beneficial effect of ticagrelor for more than 12 months is uncertain even though 25% of patients have been treated for more than 12 months. However, a large trial is already planned to evaluate long term treatment effects of ticagrelor in patients treated longer than 12 months and the Applicant will provide these data for CHMP review as a post-marketing commitment. In addition, uncertainties for certain subgroups remain, particularly due to exclusion criteria in the PLATO trial. Hepatic impaired patients are not evaluated. Another issue is that a beneficial effect of ticagrelor could have been observed due to a lack of efficacy in poor metabolisers of clopidogrel due to genetic polymorphism or concomitant PPI use. PPI treatment did not have an impact on the overall efficacy of ticagrelor as compared to clopidogrel. Upon closer inspection, event rates were larger in patients in the clopidogrel treatment arm that concomitantly received PPI treatment versus those who did not take PPI. Also in ticagrelor patients, more endpoints was noted in survival curves for patients using PPI versus not using PPIs. However, this is probably due to confounding by indication, as these patients were slightly older (0.4 years), were more often intended for invasive management (80% vs 68%), had more often an index diagnosis of STEMI or NSTEMI vs UA/other, and were more often on concomitant statin treatment. In addition, the pharmacodynamic properties of ticagrelor (pH independent absorption, no CYP2C19 activation) suggest that PPI interaction is unlikely.

Risks

- Unfavourable effects

Bleeding is the major risk associated with anticoagulants. Although the overall bleeding risk is only numerically higher and not statistically significantly increased as compared to clopidogrel, the non-procedural bleeding risk is significantly higher with ticagrelor (2.5% vs. 2.0%). In addition, PCI related bleeding risk is also increased (1.0% vs. 0.7%). This could indicate that the intrinsic bleeding risk with ticagrelor is higher than with clopidogrel, which can be expected with a higher level of platelet aggregation inhibition. And that ticagrelor treatment can be time critical in invasive management in terms of bleeding risks. For instance, this would be in congruence with the observed higher bleeding risk in patients discontinuing ticagrelor treatment within 96 hours before CABG treatment. However, these clinical findings are inconsistent with the pharmacological evaluated lower %IPA (Inhibition of Platelet Aggregation) already observed after 24 hours with ticagrelor compared to clopidogrel. Identification of bleeding risk based on Hb concentration and chest tube drainage showed that bleeding risk was similar for patients treated with ticagrelor and clopidogrel. This means that ticagrelor should also be discontinued 7 days prior to CABG. When major bleedings and minor bleedings are combined the bleeding risk is also increased. The clinical efficacy in the North American region (10% of the patients) is found to be lower with ticagrelor (HR 1.27 [95% CI 0.92, 1.75]), according to the Applicant due to use of higher doses of ASA in many cases. This was also observed for higher doses of ASA in other regions. Also for the total patient group, the stroke endpoint demonstrated an unfavourable effect (HR 1.17 (0.91-1.52, P=0.2249). However, this endpoint is underpowered as not many of these endpoints have occurred. In addition, specific adverse events have been identified, such as dyspnoea, cardiac arrhytmias, increased uric acid and renal events, which are likely to be associated with the ADP-mediated mechanism. Also a higher incidence of adverse events in renal impaired patient was found.

- Uncertainty in the knowledge about the unfavourable effects

The pivotal trial was not a placebo controlled trial, so adverse events could only be compared to clopidogrel. This is however justified as a placebo controlled trial would be unethical. The Applicant could not identify the mechanism of dyspnoea with ticagrelor. This will be further evaluated post-marketing and it is reflected in the RMP. Likely this is ADP mediated as has been postulated for cangrelor. Concerning the risk for cardiac arrhythmias (also likely to be ADP mediated), no clear effect was noticed in the pivotal trial. However, AEs possibly related to brady-arrhythmias (13.4% vs. 13.1%) were slightly increased with ticagrelor. Based on the Holter study bradycardia and dropped beats were also slightly increased. A clear conclusion on this can therefore not be made and the issue will be further investigated in additional pharmacovigilance activities as specified in the RMP. However, exact mechanisms for believed ADP mediated adverse events still remain unclear.

Although hepatic events were similar, 110 patients (ticagrelor 62 vs. clopidogrel 48) were evaluated for potential liver injury as they had elevated liver enzymes. However, these cases often represented a moderate hyperbilirubinaemia with a mild contribution of conjugated bilirubin (<20%) without signs of cholestasis or hepatocellular liver injury. Absolute values and change from baseline in liver serum ALT, AST, ALP, and total bilirubin were generally similar over time for the ticagrelor and clopidogrel treatment groups, and there was a similar frequency of liver function test abnormalities in the 2 treatment groups. However, an imbalance in the number of patients with bilirubin increase >2xULN (ticagrelor 25 vs clopidogrel 10) was still noticed. Of the patients with available samples for genotyping, most were homozygous for UGT1A1 polymorphisms known to be associated to Gilbert's Syndrome.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

Brilique, co-administered with acetylsalicylic acid is indicated in preventing of thrombotic events in patients with ACS (UA, STEMI and NSTEMI). Patients with STEMI and in particular NSTEMI have a poor short term prognosis if not treated optimally and are therefore treated aggressively. A reduction in recurrent MI, and CV death or overall death is of particular importance when evaluating drugs in the treatment of ACS. A reduction in these endpoints could outweigh some of the severe adverse events typically associated with the investigated drug. Bleeding is the most important risk to be evaluated with these kind of products. Particularly the major bleedings risk is of importance, as this can lead to a considerable risk of morbidity, or even death.

- Benefit-risk balance

In the case of ticagrelor a clear reduction in MI and CV death as well as overall death has been demonstrated when compared to clopidogrel. This clear beneficial effect outweighs the slightly higher risk for major bleedings, considered to be an acceptable risk in this high risk patient group. However, particular precaution should be given in certain situations where bleeding risk can be considerably increased, as there are signs that treatment with ticagrelor is more time critical in relation to invasive management (for instance CABG) than clopidogrel. This could be different for STEMI and NSTEMI patients due to different severity and different management of these patients. However, further comparison between these two groups of patients demonstrated a similar bleeding risk.

Discussion on the benefit-risk balance

The large PLATO trial has demonstrated that ticagrelor is more beneficial in reducing the number of primary endpoints of CV death, MI and stroke, although this is totally contributed by the CV death and MI endpoints. The effect on stroke is not found to be beneficial, although not statistically significant, but warrants some concerns. Treatment of patients with a previous history of intracranial haemorrhage

has been contra-indicated in the SmPC as these were contra-indicated in the PLATO trial and has been contra-indicated in the SmPC of prasugrel. A beneficial effect has been noticed for patients undergoing PCI irrespective of the timing of the PCI. Post hoc analyses showed that consistent benefit was also observed according to invasive or non-invasive treatment, with a slight advantage for medically managed (non-invasive) patients. Treatment with ticagrelor and timing of invasive management could be of particular importance in relation to bleeding risk, because major bleedings were noticed more frequently in patients undergoing PCI (probably due to early invasive management (within 24 hours)) and for CABG procedures too close to discontinuation of ticagrelor. Despite a difference of invasive management between STEMI and NSTEMI patients no great differences in bleeding risk was identified. The claimed faster offset of platelet aggregation of ticagrelor in comparison to clopidogrel by %IPA offset (higher within 24 hours) after discontinuation of the drug seems only to be theoretical. Other markers of bleeding risk such as Hb concentration and chest tube drainage showed that bleeding risks were similar between ticagrelor and clopidogrel. This means that ticagrelor should also be discontinued 7 days prior to CABG. Apart from the bleeding risk some typical adverse events were noticed with ticagrelor already during the phase II trial. Although the higher incidence of dyspnoea is not considered as severe that this would lead to a negative benefit/risk (although slightly more discontinuations were noticed), it is of importance to identify the mechanism of this issue. With a similar product cangrelor this adverse event was also noticed and it was postulated this was likely to be related to an ADP effect. A possible higher incidence of cardiac arrhythmias (also likely ADP mediated), in particular the bradycardia, were identified during phase II trials and could lead to severe consequences. Although bradycardia was also noticed with a slightly higher incidence in the Holter substudy, no higher incidence of severe adverse events could be noticed in the PLATO trial. Nevertheless, cardiac adverse event warrant further attention in the future, and it is reflected in the RMP, as no clear conclusions on this could be made. Also other probably ADP-mediated AEs were identified, such as rise in uric acid and renal events related to rise in serum creatinine, and other potential risks, like DILI (Drug Induced Liver Injury) or uric acid nephropathy, and should be followed within the RMP. A remarkable finding is the lower efficacy of ticagrelor in the North American population, although this is of less importance for the marketing authorisation in the EU as enough patients remain for evaluation of the target EU population (only 1300 patients in US). A higher ASA dose was the main identifiable reason of the negative effect also for non-US patients. In addition, there seems to be a lack of efficacy in the unstable angina subgroup. However, these patients are not identifiable before treatment. The combined UA/STEMI patient group showed similar benefit/risk to the STEMI patients group. A limitation of the pivotal trial is that the long-term evaluation is largely limited to 12 months, but a trial is planned for evaluation longer than 12 months. The SmPC reflects that patients undergoing CABG should stop their ticagrelor treatment with at least an interval of 7 days between discontinuation of ticagrelor and start of CABG, similar to the discontinuation warning in the SmPC of clopidogrel and prasugrel. Further, patients with moderate to severe hepatic impairment, and history of intracranial haemorrhage are not included in the study and are contra-indicated in the ticagrelor SmPC. The higher incidence of adverse events in renal impaired patients and additional information on bleeding risk in certain patients or situations have been included in section 4.4 of the SmPC.

Risk management plan

A risk management plan (version 4, 21 Sep 2010) was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

and

no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Brilique co-administered with acetylsalicylic acid (ASA) in the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) was favourable and therefore recommended the granting of the marketing authorisation.

Brinavess

Beneficial effects

In the pooled data of the general AF population (ACT I/III, n=390), vernakalant administration resulted in significantly higher conversion rate to SR (51.1%) compared to the placebo treated group (3.8%) (% difference 47.3% 95% CI: 40.2- 54.4), within the first 90 minutes. Median time to conversion in the vernakalant group was 10 minutes compared to 31.5 minutes in the placebo group. For the patients who converted, rate of maintenance of sinus rhythm was 97.2% at 24 hours and 93% at 7 days. In the subgroup of patients with AF duration <48 hours, the rate of conversion to SR was significantly higher in the vernakalant group (61.2%) compared to the placebo group (4.9%). Vernakalant administration did not affect the response of the patients to subsequent electric cardioversion, in case of vernakalant failure. In post-cardiac surgery patients (ACT II, n=150), vernakalant administration resulted in significantly higher conversion rate to SR (47%) compared to the placebo treated group (14%) (% difference 33% 95% CI: 19.3- 46.7). The median time to conversion was 12.4 minutes in the vernakalant group compared to 29.7 minutes in the placebo group. For the 48 patients with AF (AFL) who converted to sinus rhythm, rate of maintenance of sinus rhythm at 24 hours was 59.5% and 56.9% at 7 days compared to 50.0% in the placebo group at 24 hours and time of hospital discharge (or within 14 days).

- Uncertainty in the knowledge about the beneficial effects.

No robust claims can be made on maintenance of SR beyond 24 hours as no continuous ECG monitoring was available beyond that time. In the three placebo-controlled studies, the recruitment criteria were quite broad, but that did not translate into adequate representation of some subgroups of interest, in particular patients with NYHA III/IV, and those co-administered rate or rhythm control

AADs. These subgroups are currently contraindicated in the SPC. The efficacy endpoint was measured at 90 minutes, thereafter other interventions were allowed. A specific study was conducted to assess conversion in post-cardiac surgery patients. Recruited patients were of shorter duration AF, this difference in duration is currently reflected in the indication. Results of the general population of AF are better than those reported in post-cardiac surgery patients, but these were still significantly better than placebo. The actively-controlled study against amiodarone showed vernakalant to be more rapid than amiodarone, with the caveat that amiodarone may not have been the best comparator considering its known delayed onset of action. Still, compared with historical data, the overall rate of conversion to SR reported with vernakalant appears at least comparable to that reported with amiodarone, flecainide or ibutilide with a shorter time to conversion, but definite conclusions are not possible without direct comparative data with those latter agents.

Risks

- Unfavourable effects

The safety database of vernakalant appears adequate with 507 patients administered the full dose (3 mg/kg followed by 2 mg/kg) and 241 patients administered the first dose (3 mg/kg). Due to the short half-life of vernakalant, most of the AEs are observed during the first 2 hours of administration. The most common treatment-related AEs reported during this period are dysgeusia, sneezing, parasethesia, nausea and hypotension. These AEs were described as mild or moderate and were not treatment-limiting. The most frequently reported serious related AEs were hypotension (1% vernakalant vs 0.3% in placebo), bradycardia (0.4% in vernakalant vs 0 in placebo) and AV block (0.3% vernakalant vs 0 in placebo). One case of death related to vernakalant was reported, however, the patient was erroneously recruited and afterwards administered vernakalant in spite of the stopping rules. Death was preceded by hypotension and ventricular fibrillation. An important issue is the proarrhythmic potential. Data clearly show QTcF prolongation with placebo-subtracted peaks of +22.1 msec (95% CI: 18.9-25.3) at minute 10 and +18.8 msec (95% CI: 15.6-22) at minute 35, returning to baseline by 50 minutes. Substantially more patients in the vernakalant group were observed with QTcF prolongations of ≥30 msec and ≥60 msec compared to the placebo group till the second hour after administration, although the absolute number of patients with a QTcF prolongation of ≥60 msec was low. Only one event of TdP was recorded in which the causation is confounded by the co-administration of ibutilide. The risk of developing AFL was significantly higher following vernakalant (6.1%) than placebo (1.6%)(percent risk difference 4.5: 95% CI 2.3 to 6.7), but no patient with AFL following treatment with vernakalant injection developed 1:1 atrioventricular conduction. Background use of rhythm control agents was associated with a higher risk of developing AFL (percent risk difference of 6.8, 95% CI 4.0 to 9.7).

- Uncertainty in the knowledge about the unfavourable effects

The actual representation of different subgroups of patients in safety database (e.g non-white, slow metabolisers or with associated medical conditions) may not be sufficient. Also clinical and non-clinical data on repeat administration is lacking. Non-clinical data support a lower potential of vernakalant to induce TdP than other AADs. However, the current safety database is too limited to give a realistic estimation of the risk. Also, patients with CHF did show an increased incidence of ventricular arrhythmias compared to placebo, although the incidence was low and VF was noted only once in a patient who should have been contraindicated. In summary, the proarrhythmic potential of vernakalant appears low, but in high-risk patients the risk is still present and more clinical data will show whether the risk for TdP is indeed as low as now suggested. Patients with congestive heart failure appear to be also at more risk for hypotension. The experience is mainly based on patients with NYHA I/II, whereas NYHA III were minimally represented and NYHA IV excluded. In turn, a low baseline SBP (<105 mmHg) and a history of CHF were the most important factors that increased risk of hypotension. The incidence of bradycardia in the 0-2 hour period was slightly higher in the vernakalant group (5.4%) compared to placebo (3.8%) (percent risk difference 1.6; 95% CI:-1.1, 4.3), but this is probably driven by patients who converted to SR.

- Benefit-risk balance

Vernakalant, concentrate for solution for infusion, is effective in converting AF of short duration to SR in non-surgical as well as post-cardiac surgery patients. The conversion rate is in line with that reported with other AADs such as flecainide, ibutilide and amiodarone. Median time to conversion is very short making it a relevant option for highly symptomatic patients, especially when compared to amiodarone with longer time to conversion, as observed in the AVRO study. However the target group is probably different from that of amiodarone. Efficacy was accompanied by AEs mainly during the first

2 hours of administration. The most frequently reported AE (dysegeusia, sneezing and parasthesia) did not impact on the tolerability of the drug, but their mechanism is not studied. The more serious AEs: hypotension or bradycardia are well defined for the general population, though also the mechanism is not known. Patients with low blood pressure or bradycardia at baseline appear to be at higher risk for developing these AEs. Patients with congestive heart failure (NYHA I/II) are another population at risk, showing a higher risk of hypotension and ventricular arrhythmia. There is limited experience in severer forms of CHF, but based on the current experience in NYHA I/II, vernakalant use is contraindicated in these patients. The arrhythmogenic potential of vernakalant appears limited based on both clinical and non-clinical data, however no robust conclusions can be made due to the limited experience. Compared to flecainide, there is also a higher incidence of conversion of AF to AFL, but this was not accompanied with 1:1 conduction.

- Discussion on the benefit-risk balance

In summary the benefit-risk balance of vernakalant for the claimed indication is considered positive. Questions remain regarding its safety in patients with moderate and severe heart failure and its concomitant administration with other anti-arrhythmic agents, but these issues are addressed by appropriate labelling. More clinical data are needed before final conclusions can be drawn on its proarrhythmic potential. For all identified and potential risks a Post-authorisation Registry study is requested. The aim of this PASS is to better characterise the safety profile of vernakalant in the context of normal clinical use of the product. Amongst others, the incidence of hypotension and ventricular arrhythmia will be estimated. In addition to the identified and potential risks, the following events of special interest will be collected: atrial flutter with 1:1 atrioventricular conduction of duration >10 seconds and ventricular rate >200 and bradycardia requiring mechanical pacing (temporary or permanent). The study is a prospective, observational study of vernakalant iv that will be conducted in multiple European countries. Countries under consideration include Denmark, France, Germany, Italy, the Netherlands, and Spain but final selection is conditional on a number of factors, including, but not limited to, the actual date of product launch in each country and rate of market uptake of vernakalant iv. The list of countries selected for the registry will be included in the draft registry protocol submitted to the CHMP by October 2010. Patients will receive vernakalant iv at the discretion of their physicians. Data collection will be performed during and shortly following vernakalant administration. The registry will enrol 2,000 patients across participating EU countries. The sample size was selected in order to have sufficient statistical precision as expressed by a 2-sided, 95% confidence limit around the expected incidence rate for each medically significant health outcomes of interest (HOIs).

The incidence of each medically significant HOI during the first 24 hours post-vernakalant administration among subjects randomised to receive vernakalant iv in the pooled clinical trial database (n=889, including the AVRO Study) ranged from 0% to 0.22% for each HOI.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

plus

the following additional risk minimisation activities were required: all Healthcare Professionals (HCP) involved in the administration of Brinavess are provided with a healthcare professional information pack.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Brinavess in the rapid conversion of recent onset atrial fibrillation to sinus rhythm in adults

- for non-surgery patients: atrial fibrillation ≤ 7 days duration
- for post-cardiac surgery patients: atrial fibrillation ≤ 3 days duration was favourable and therefore recommended the granting of the marketing authorisation.

Daxas

Benefit

Patients with severe COPD remain symptomatic and poorly controlled despite available treatment. Roflumilast has a novel mode of action working in a different way than any of the current COPD treatment. Hence, roflumilast could be a useful adjunct to currently existing COPD treatments.

Despite reaching statistical significance, the effect of roflumilast on the primary endpoint is modest. However, these effects were observed in a population with severe COPD (type chronic bronchitis) patients with very poor lung function and minimal reversibility at baseline. In addition, the effect of roflumilast on exacerbations was reached on top of bronchodilators, not in addition to placebo.

The lack of standardisation for the concomitant medications and potentially the lack of standardisation of the study population in the treatment arms were considered as a potential bias to the results. In addition, the current first line treatment (combination of LABA / ICS) was not used in the trials, neither as concomitant medication nor as a comparator. Hence, at the CHMP's request, the applicant commits to conduct a controlled study to evaluate the use of roflumilast as an add on therapy on top of LABA and ICS in the population defined in the indication of the current SPC. The design of the study should be appropriate to demonstrate a clinically relevant effect of roflumilast as add-on therapy.

An ad hoc expert group meeting was convened by the CHMP. Overall, the experts agreed that the clinical relevance of the effect of roflumilast on FEV1 was difficult to judge based on the available data since the current first line treatment was not used in the trials, neither as concomitant medication nor as a comparator. However, taking into account the severity of the disease in the patients enrolled in the trials, in which a very small variation of FEV1 is expected according to the natural history of the disease, some experts felt that the effect shown by roflumilast on this parameter might not be negligible. With regard to the effect of roflumilast on the exacerbation rate endpoint, the experts agreed that this was closer to demonstrate clinically relevance in patients with severe to very severe COPD, high exacerbation rate and chronic bronchitis.

Risk

The following adverse events were documented with higher rates in the roflumilast arm than in the placebo arm: weight decrease, diarrhoea, nausea, headache, decreased appetite, back pain, dizziness and insomnia. The intensity of these events was generally of mild to moderate intensity. Weight loss is of particular concern as this adverse event is associated to a worse prognosis in COPD. In pivotal studies, the rate of AEs leading to withdrawal was superior in the roflumilast group than in the placebo group. In addition, a relationship between risk of triggering suicide and roflumilast cannot be excluded. Hence, at the CHMP's request, the Applicant will conduct a long-term comparative observational safety study to further assess the risks associated with the use of roflumilast.

- Benefit-Risk Balance

There is a medical need for new treatments for COPD. The availability of a new anti-inflammatory treatment in severe COPD may be seen as an additional chance for severe COPD patients.

Both roflumilast pivotal studies had a positive outcome on the primary endpoints. The effect of roflumilast is modest and the clinical relevance of these finding remain unclear. The limited reduction in exacerbation rate is consistent with the modest effect observed with roflumilast. The treatment benefit on the lung function parameter is below the usual limit of minimally clinically important difference. Nevertheless, this modest benefit may be of interest in a severe to very severe population and this effect was reached on top of bronchodilators. Hence, the CHMP requested to restrict the indication to the subgroup of patients with severe COPD disease, type chronic bronchitis and frequent exacerbations (at least 2 exacerbations in the last year).

The main risks associated with the use of roflumilast are diarrhea, nausea and weight loss. A relationship between risk of triggering suicide and roflumilast cannot be excluded.

Overall, the available data justify the use of roflumilast in the restricted subgroup of patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations. In order to better demonstrate the clinical relevance of the effect of roflumilast as add-on therapy, the Applicant will conduct a controlled study to evaluate the use of roflumilast as an add on therapy on top of LABA and ICS in this population. In addition, the Applicant will conduct a long-term comparative observational safety study to further assess the risks associated with the use of roflumilast.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see section 3.6.2.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Daxas in the following indication:

Daxas is indicated for the maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV1 post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment.

was favourable and therefore recommended the granting of the marketing authorisation.

Humenza

Benefits

The real benefits of Humenza can only be assessed by its use during a pandemic. At present the potential benefit can only be evaluated based on detailed characterisation of immunological responses to vaccination with AF03/H1N1 obtained in the three Phase II clinical studies and with supportive data obtained with AF03/H5N1

A single dose of 3.8 µg HA/AF03 has been shown to be suitably immunogenic in children aged 3-17 years old and adults 18-60 years old. Similarly, in subjects aged 6-35 months, it was found that one

half adult dose will be adequately immunogenic. Based on narrow age strata immunogenicity analyses, only two-dose schedule can be advocated in elderly aged > 60 years old.

Data from the three main studies show that the vaccine induces a strong immune response in all subjects.

Therefore the expected benefit of Humenza is to provide some protection against clinically-apparent infection due to A(H1N1)v.

Risks

The safety and reactogenicity profile of the vaccine resembles what was seen for other pandemic vaccines that contain an adjuvant like MF59 and AS03.

However, safety data package of Humenza submitted so far suffers from similar limitations as do other pandemic vaccines, including lack of data from high-risk groups and diseased subjects, lack of data on concurrent use with other vaccines or drugs, and small database unable to detect rare adverse events. A sound RMP and PhVS has been put in place in order to minimise the potential risks. Although unspecific for Humenza, the occurrence of erythema, fever, shivering and malaise in a significant proportion of vaccinees following Humenza (especially following second dose) highlights the identified risk.

Cases of pregnancy with favourable outcomes were noted in supportive study, but the number of cases was very small and no firm conclusion can be drawn. The recommendation will be updated as soon as data on use of Humenza in pregnancy become available.

AF03 is regarded as a new adjuvant and licensure of Humenza does not build on an approved mock-up vaccine. In this respect, supportive safety follow-up and booster data with AF03/H5N1 vaccines are considered very helpful. Overall, no safety concern was identified following the booster vaccination, and within the time period of up to 12 month follow up after primary series and 6 month follow-up after booster vaccination.

The specific commitments include collection of safety, immunogenicity and effectiveness data from the ongoing and planned clinical studies.

Balance

Based on all the quality safety and efficacy data specific to the pandemic influenza A(H1N1)v strain and on supportive data provided with the H5N1 strain, it is considered that in the current pandemic situation the benefits outweigh the risks that may be associated with the use of the vaccine in accordance with the SPC.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.3.

The CHMP considers that the eligibility in accordance with Article 2(2) of Council Regulation (EC) No 507/2006 together with the criteria of conditional Marketing Authorisation in accordance with and 4 of Council Regulation (EC) No 507/2006 are fulfilled.

Furthermore, the CHMP took note that the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed. Already available paediatric data of studies subject to this plan are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered majority decision that the risk-benefit balance of Humenza in the "Prophylaxis of influenza in an officially declared pandemic situation" was favourable and therefore recommended the granting of the conditional marketing authorisation.

A divergent position was expressed by some members of the CHMP taking the view that "the safety database as presented by the applicant is not considered sufficient to conclude on a positive Risk/Benefit ratio for Humenza in the current situation".

Prolia

Risk-benefit assessment

Benefits with denosumab are:

- For the indications applied for, administration is simple as the drug is administered as a subcutaneous injection of a fix dose once every 6 months, and many patients can probably be trained to administer

the injections themselves. The treatment effect of denosumab is reversible and study data indicate that bone formation returns to base levels within one year after the cessation of denosumab therapy.

- For treatment of osteoporosis in postmenopausal women at increased risk of fractures, the pivotal study for this indication was adequately sized, designed and performed and the efficacy results were similar to or better than what has earlier been demonstrated for other drugs approved for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The risks for interference with the immune system seem to be moderate according to data from large clinical studies. Treatment of bone loss associated with hormone ablation in women with breast cancer at increased risk of fractures is not considered to be a separate indication as these patients are considered to be postmenopausal and at increased risk of fracture and thus to be included in the PMO indication.

- For treatment of bone loss associated with hormone ablation in men with prostate cancer, efficacy was clearly shown as fracture incidence reduction and this effect is clinically relevant. This positive effect must be weighed against the risks of interference with the immune system. The men in the pivotal study for this indication exhibited an overfrequency of adverse events of neoplasms, mainly attributed to benign neoplasms, especially basal cell cancer. In addition, a high risk group for fractures needs to be better defined within this indication.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered By consensus that the risk-benefit balance of Prolia in the following indication:

"Treatment of osteoporosis in postmenopausal women at increased risk of fractures. Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures. Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures."

was favourable and therefore recommended the granting of the marketing authorisation.

Rapiscan

Benefits

- Beneficial effects

Regadenoson is expected to be used as adjunct to myocardial perfusion imaging as a stress agent. Based on its pharmacological properties this is appropriate. Whilst the pharmacology is similar to adenosine, it has little activity against A1, A2b or A3 receptors with significant specificity at the A2A receptor for agonistic effect. Given this background and the data from the pivotal trials, its non-inferiority to adenosine in performance as a adjunct to radiopharmaceutical has been shown. One of the advantages of regadenoson is fewer risks: less bronchoconstriction and less high grade Av block than with adenosine. From an administration perspective the main benefit of regadenoson over adenosine would be that it can be administered as a bolus instead of an infusion which would increase the convenience for patient and technologist.

- Uncertainty in the knowledge about the beneficial effects.

Concerns related to statistical analysis in both pivotal studies have been addressed by the applicant by providing additional analysis. Based on the data provided on regadenoson there is little uncertainty about its performance as a stress agent.

Risks

- Unfavourable effects

The risk of AV or sinus node dysfunction in predisposed individuals still exists, although, it is much lower for regadenoson than for adenosine. The major AEs reported are dyspnoea and headache and these have been addressed in the SPC. Bronchospastic tendency appears lower with regadenoson; reduction in FEV1 was still observed. However, this could not be quantified due to the small size of the studies

- Uncertainty in the knowledge about the unfavourable effects

Based on the data provided, there are a few uncertainties regarding safety of regadenoson in patients with renal failure and in patients with COPD. The data currently available are from small studies. Post marketing studies are ongoing for further evaluation of risk in renally impaired subjects and in those with COPD (chronic obstructive pulmonary disease). The magnitude of effect will be better judged with increasing exposure as data become available from these studies. The applicant has committed to submit the study reports as follow up measures.

Risk balance

Based on the data, there are no safety issues; missing information will be addressed by post marketing studies. Non-inferiority to adenosine has been shown in two pivotal trials. Clarifications regarding diagnostic value and the statistic used (kappa) for demonstrating non-inferiority have been adequately addressed by the applicant and overall safety reports including the EU-RMP and Pharmacovigilance systems have been updated. The benefit-risk balance is favourable for regadenoson.

- Discussion on the benefit-risk balance

As non-inferiority to adenosine has been shown, it is concluded that regadenoson performs as well as adenosine as an adjunct to the radiopharmaceutical for detection of stress induced ischaemia. Its safety profile is acceptable despite a number of uncertainties, which will be further explored in post marketing studies. The benefit risk balance is considered positive for the indication "Rapiscan is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.

" and the CHMP recommends approval as standard marketing authorisation.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

Additional pharmacovigilance planning was requested to adequately monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Rapiscan in the in the following indication:

"Rapiscan is a selective coronary vasodilator for use as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress"

was favourable and therefore recommended the granting of the marketing authorisation .

Ruconest

Benefits

- Beneficial effects

A beneficial and clinically relevant effect was shown for rhC1INH in the primary endpoint, time to beginning of relief, in both randomised studies compared to placebo. The data were statistically robust and supported by the outcome of the secondary endpoint and by pharmacodynamic data. Exploratory endpoints were also in most parts in favour of rhC1INH. The median time to beginning of relief observed is comparable to that reported for plasma-derived C1INH and also for icatibant.

Dose-finding was based on previous experience with plasma-derived C1INH and from pharmacokinetic and pharmacodynamic studies in asymptomatic HAE patient. Two doses (50 and 100 U/kg) were evaluated within the RCT studies and this choice is considered adequate. The data from the RCT studies support the choice to continue the clinical programme with the 50 U/kg dose with the option to

give an additional dose within four hours from the first administration. The posology to administer a dose of 50 U/kg in adults up to 84kg, and a dose of 4,200 U in adults over 84 Kg, i.e. a weight–based cut-off of 84 kg is endorsed.

The effect of treatment on patients with severe laryngeal oedema across all clinical studies have been analysed and the data indicate that rhC1INH is efficacious also in these attacks, however, time to beginning of relief appears to be somewhat longer than in other locations. Additional efficacy data provided support the proposed dose of 50U/kg demonstrating that the median time to beginning of relief of symptoms was the similar for potentially life-threatening attacks (PLA) as for all attacks, Therefore the proposed dose of 50 U/kg for PLA attacks as for other sites is endorsed.

Uncertainty **in the knowledge about the beneficial effects.**

The effect of rhC1INH appears to be similar for different anatomical locations of the attack, and also across studied subgroups. However, the available data are limited.

Efficacy has been studied in patients receiving treatment for up to 20 HAE attacks. Nevertheless, uncertainties remain as to whether the efficacy will wane on long term repeated administration in subjects who develop antibodies against rhC1INH.

Information from treatment in special populations is limited or lacking.

Risks

- Unfavourable effects

The safety data base is still limited. In total, 165 subjects (14 healthy volunteers, 12 asymptomatic and 139 symptomatic HAE patients) had been exposed to a total of 405 administrations of rhC1INH.

The major risk already identified is the risk of allergic reactions in patients with known or unknown allergy to rabbits. One healthy volunteer experienced a serious allergic reaction to rhC1INH and was shown to have high IgE titres against rabbit allergens. Once identified, this risk may be possible to handle by preventive measures such as testing patients before exposure. This information on the use of commercially available tests to identify patients has been added to the SPC.

Recombinant protein products such as rhC1INH administered to human subjects may elicit antibodies against the recombinant protein, its endogenous counterpart, and against HRI in the drug product. The immunogenic potential of rhC1INH has been studied within the clinical programme and methods to detect antibodies have been developed. Although increased levels of antibodies sporadically have been detected, there has been no indication this far that they are of clinical relevance in terms of either efficacy or safety.

Concerns have been raised that rhC1INH, which is given in higher concentrations than pdC1INH, would have a thrombogenic potential. This has been evaluated by the applicant during the clinical development without indications that this may be the case.

The pattern of other adverse events does not evoke any new safety concerns. The most common adverse events reported were infections (mainly upper respiratory infections and sinusitis); these adverse events were more common in the active treatment group. Rash and pruritis was also more common in the active treatment groups (a total of 5 reports). Headache and abdominal pain was also commonly reported, with the same rate in actively and placebo-treated patients. No deaths occurred during any of the clinical studies. Apart from the allergic reaction discussed above, none of the reported SAEs appear directly related to the treatment.

- Uncertainty in the knowledge about the unfavourable effects

The safety database is limited and further safety data will have to be collected in a post-authorisation safety study. Such measures have been proposed by the applicant. In addition the applicant will make available immunogenicity testing (for anti-C1INH and anti-HRI antibodies) for cases who present with features suggestive of an immune response. The applicant is also developing a skin prick test for rhC1INH. Both of these plans are strongly supported. In view of the complexity of the planned immunogenicity testing the applicant is requested to provide educational materials for this.

Antibody development to rhC1INH could lead to reduction in efficacy, and if cross-reactive to pdC1INH might lead to worsening of HAE and even reduction of loss of efficacy from pdC1INH treatment. Although there is no evidence of this from the efficacy data available to date, it remains a potential problem.

A further concern is the possible cross-reactivity between cow's milk and rabbit milk. Because the homology between these species is low and similar to the homology of camel and horse milk to cow's milk, the likelihood for cross-reactivity is predicted to be low. However cross-reactivities can occur with serious consequences and therefore a warning in section 4.4 of the SPC has been added for those with clinical evidence of cow's milk allergy.

Benefit-risk balance

- Importance of favourable and unfavourable effects

rhC1INH is intended for the treatment of acute HAE attacks a rare and potentially life-threatening condition. Efficacy has been clearly demonstrated by generating clinically relevant and statistically robust data. The importance of these favourable effects is supported through:

  - continued availability of supply due to independence of donor plasma;
  - targeting the additional mediators of swelling in angioedema other than bradykinin;
  - not being a blood-derived product thereby removing the potential risk of blood-born pathogens.

rhC1INH unfavourable effects relate to the fact that pre-exiting allergy to rabbit dander was identified as the probable cause of the severe allergic reaction in the healthy volunteer. Patients who are rabbit allergic are those who are likely to have a major allergic reaction on their first treatment with rhC1INH. This very serious event, particularly if it occurs in an attack of laryngeal oedema could be fatal. Avoiding treating such cases is very important and the identification of such cases in clinical practice will be central to the safe use of the product. This should be achieved with the contraindication in section 4.3 and the further advice in section 4.4 of the SPC.

The importance of anti-rhC1INH would be the potential reduction in efficacy with rhC1INH and possibly also with pdC1INH treatment. The availability of alternative treatment with icatibant makes this possibility one in which the patient will still be able to receive treatment. Further information from the PASS study will help to address these uncertainties.

The importance of anti-HRIs is that these antibodies may lead to infusion reactions and serum-sickness symptoms. These effects would lead patients to discontinue rhC1INH and switch to another treatment.

- Benefit risk balance

Efficacy has been clearly demonstrated for the treatment of this rare and potentially life-threatening condition. Antibody development to rhC1INH and to HRI has not been demonstrated to result in clinical sequelae to date. The importance of these unfavourable effects is considered to be limited to those

who have IgE to rabbit allergens and to those who mount an immune response to rhC1INH and/or HRIs.

Important for clinical practice is to avoid using the product in patients who are rabbit allergic due to potentially serious allergic reactions. This very serious event, particularly if it occurs in an attack of laryngeal oedema could be fatal. Avoiding treating such cases is very important and the identification of such cases in clinical practice will be central to the safe use of the product. Rabbit allergy constitutes a contraindication and the SPC proposes that before initiating treatment with rhC1INH, patients should be tested for the presence of IgE antibodies against rabbit allergens using a validated test for IgE antibodies against rabbit epithelium (dander) e.g. ImmunoCap system. Only patients who have been shown to have negative results for such tests, should be treated with rhC1INH. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.

A potential risk of cross-reactivity of IgE specific for cow's milk in those who have clinical evidence of IgE-mediated cow's milk allergy remains. This has been addressed in the SPC.

- Discussion on the benefit-risk balance

The benefit of rhC1INH is a ready supply of a new treatment for acute attacks in HAE for which efficacy has been clearly demonstrated. For the safety concerns that have been identified (namely allergic reaction in those with pre-formed IgE antibody to rabbit dander) it is considered possible to minimise the risk of such events occurring by having rabbit allergy as a contraindication and by the requirement for a negative test for IgE to rabbit dander to be obtained in a patient prior to initiation of treatment. These points are clearly highlighted in the SPC.

Specific educational material for healthcare professionals as well as patient alert cards will be provided by the applicant.

The potential for a patient to develop antibodies to rhC1INH and/or to HRIs following repeated treatment remains a potential risk and further information on this will be made available post authorisation. In particular, the applicant commits to make anti-C1INH antibody tests available for any HAE patient on Ruconest meeting any of the following criteria:

- In two consecutive acute angioedema attacks there is a need for a dose greater than 50U/kg rhC1INH in any HAE patient that previously responded to treatment with 50 U/kg rhC1INH.
- In two consecutive acute angioedema attacks a failure to respond to rhC1INH treatment within 4 hours despite adequate dosing of 50 U/kg in any HAE patient who previously responded to treatment with 50 U/kg rhC1INH.

In addition, the applicant commits to make anti HRI antibody tests available for any HAE patient on Ruconest meeting any of the following criteria:

- Type III hypersensitivity reaction (skin, joints or kidney symptoms) in temporal relation with a Ruconest administration which after investigation of other causes cannot be explained by exposure and reaction to other allergens.
- Type III hypersensitivity in temporal relation with two consecutive administrations of Ruconest.

The company also commits to expedited reporting for cases concerning development of antibodies to C1INH and/or HRIs.

An important element of the long-term risk management strategy is the commitment to perform a post authorisation safety study, for which the protocol will be agreed with the CHMP prior to study start. This study should also include follow-up of HAE patients repeatedly treated with rhC1INH for acute angioedema. In addition to the testing provided in the PASS study the applicant commits to make

certain antibody tests (anti-C1INH and HRI) available for patients who have not consented to the PASS study and who fulfil the criteria for further immunogenicity investigation.

These data will be important for the monitoring of the benefit risk balance.

In conclusion, the benefit risk balance is considered positive.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- the following additional risk minimisation activities were required:
- See section: Risk Management Plan.

The CHMP is of the opinion that Ruconest is not similar to Firazyr within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Ruconest in the "treatment acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency" was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Ruconest not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Firazyr for the same therapeutic indication.

Sycrest

Benefits

- Beneficial effects

SCHIZOPHRENIA

In study 041004, twice daily dose of asenapine 5 mg was studied versus twice daily doses of risperidone 3 mg and placebo. The tested dose demonstrated statistically significant difference over placebo with a change from baseline to week 6 in PANSS total score of -15.86 for asenapine versus -5.27 for placebo (p=0.0024).

In study 041023, treatment with asenapine 5 mg BID resulted in a statistically significantly greater mean change from baseline to week 6 in the PANSS total score of -16.2 for asenapine versus -10.7 for placebo (p=0.0290).

In study A7501012, there was a statistically significant difference in favour of asenapine between the treatment groups with respect to the time to relapse or impending relapse ($p<0.0001$) based on a log-rank test. The time to relapse was longer in the asenapine group compared with the placebo group. Asenapine was also shown to be more effective than placebo in prolonging the time to early termination for any reason and the time to relapse or impending relapse.

BIPOLAR I DISORDER

In study A7501004, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p=0.0065 for asenapine versus placebo and p<0.0001 for olanzapine versus placebo). The mean change from baseline to Day 21 was -11.5, -7.8, and -14.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21.

In study A7501005, Y-MRS total scores were statistically significantly improved in the asenapine and olanzapine treatment groups compared with the placebo treatment group (p<0.0001 for both comparisons with placebo). The mean change from baseline to Day 21 was -10.8, -5.5, and -12.6 for the asenapine, placebo, and olanzapine treatment groups, respectively. Mean changes from baseline in the CGI-BP, severity of mania also showed statistically significant improvements in the asenapine group over placebo at Day 21. At Day 21, 42.3% of subjects in the asenapine group were responders compared with 25.2% in the placebo group. This treatment difference was statistically significant (p=0.0049). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo at day 21(p<0.0001). At Day 21, 40.2% of subjects in the asenapine group were remitters compared with 22.3%in the placebo group. This treatment difference was statistically significant (p=0.0020). A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0041).

In study A7501006, a 9-week, olanzapine-controlled, double-blind, double-dummy, multicentre, parallel group, continuation trial, both the asenapine and olanzapine groups showed improvement on the primary efficacy endpoint. The mean change from baseline to Week 12 on the Young-Mania Rating Scale (Y-MRS) was -27.3 for the asenapine treatment group and -23.7 for the olanzapine treatment group.

- Uncertainty in the knowledge about the beneficial effects.

SCHIZOPHRENIA

With respect to phase II short-term trials (041002, 041013 and 041004), no dose response could be established.

In study 041021, no statistically significant differences in the mean changes from baseline to week 6 in the PANSS total score were observed between placebo (-11.1) and asenapine 5 mg (-14.5) or asenapine 10 mg BID (-13.4). Mean change from baseline to week 6 on PANSS total score for placebo, asenapine 5 mg BID, asenapine 10 mg BID and olanzapine 15 mg QD were -11.1 (1.64), -14.5 (1.59), -13.4 (1.63), -16.5 (1.64), respectively. Compared with placebo, olanzapine treatment resulted in a statistically significantly greater mean change from baseline in the PANSS total score (-16.5, p=0.0168).

In study 041023, no statistically significant difference between asenapine 10 mg BID and placebo was observed in the mean change from baseline to week 6 in the PANSS total score (placebo [-10.7] versus asenapine 10 mg BID [-14.9], adjusted p=0.0680) using the LOCF method. Analyses of the primary endpoint using OC and MMRM analyses showed a statistically significant difference in favor of asenapine 10 mg BID [-18.5] compared with placebo [-14.0] was observed (p=0.0167).

In study 041022, no statistically significant differences (p>0.05) in the mean changes from baseline to week 6 in the PANSS total score were observed between asenapine (-9.4) and placebo (-9.9) or

between olanzapine (-11.5) and placebo (-9.9). Furthermore, no statistically significant (p>0.05) differences between asenapine and placebo or between olanzapine and placebo were observed in the mean changes from baseline to endpoint in any secondary efficacy or health outcomes measures.

Results from a retrospective meta-analysis (including short term phase III studies) was suggestive of efficacy (for PANSS total score: 2.7 points greater for asenapine versus placebo (p=0.021; 95% CI -5.0 to -0.4); for responder rates: OR=1.9, 95% CI 1.3 to 2.6; p<0.001). However, the pooled 95% CI was very close to zero. Adding in the data from the phase 2 study 041004 improved the result, with the lower bound improving to -1.5 and the p-value becoming p=0.0011. But as this combines the hypothesis generating and the pivotal data there is a higher hurdle to meet. Ideally the phase 3 data alone should provide compelling evidence of efficacy.

In the long term placebo-controlled, double-blind trial A7501012, asenapine was statistically significantly superior to placebo (p<0.001 on log-rank test). If short term benefit could be established this would provide support for long-term treatment. However, in the absence of short-term benefit having been demonstrated the study is of limited relevance.

In study A25517, statistically significant difference (p<0.001) in the mean change from baseline to week 52 in the PANSS total score was observed in favour of olanzapine. At baseline, the PANSS total scores were 92.1 for both asenapine and olanzapine groups. At week 52, the PANSS total scores were 71.0 and 64.6 for asenapine and olanzapine groups, respectively (difference: 6.54, 95% CI: 3.87-9.21).

BIPOLAR I DISORDER

No dose response studies were conducted.

In study A7501004, 42.6% of subjects in the asenapine group were responders compared with 34.0% in the placebo group at week 3. However, this treatment difference was not statistically significant (p=0.1951). A statistically significant greater percentage of subjects in the olanzapine group were responders compared with the placebo group (p=0.0011) at week 3. Additionally, 35.5% of subjects in the asenapine group were remitters compared with 30.9% in the placebo group and this treatment difference was also not statistically significant (p=0.5033).A statistically significant greater percentage of subjects in the olanzapine group were remitters compared with the placebo group at Day 21 (p=0.0159).

In study A7501008, analyses using several methods for handling missing data (LOCF, OC, MMRM) showed different results. Overall, the CHMP concluded that non-inferiority of asenapine versus olanzapine was not shown.

Risks

- Unfavourable effects

The incidences of the most common AEs were generally comparable to those seen for olanzapine except for sedation (but not somnolence) which seemed to be more common with olanzapine (15.1%), and "hypoaesthesia oral". The applicant has provided a satisfactory justification that the incidence of oral hypoaesthesia is due to the local anaesthetic activity. This seemed unlikely to be of major clinical concern although there is probably some risk of oral injury e.g. by inadvertent biting. The amount of local anaesthetic is insufficient to cause concerns relating to impairment of protective airway reflexes.

The overall AE rates were not substantially different from olanzapine. However the rates of severe adverse events, serious adverse events and adverse events leading to discontinuation were consistently higher. There was no indication of a different safety profile in the two patient populations.

The severe / serious / discontinuation AEs were predominantly in the psychiatric, nervous system and gastrointestinal (GI) system organ class (SOC). The excess over olanzapine is seen to lie almost entirely in the psychiatric SOC; there is a weak trend at best to an excess in the nervous system and none at all in the GI SOC.

Differences in psychiatric adverse event rates appear to become apparent in particular with long term treatment. This is of potential concern as treatment is often required in the long term especially in schizophrenia where treatment is often required life long. However it is agreed that a substantial proportion of reported serious psychiatric adverse events are likely to reflect hospitalizations and/or other events due to exacerbations of the illness being treated. As asenapine showed consistently less efficacy than olanzapine in the clinical trials it seemed plausible that the excess incidence in severe / serious / discontinuation AEs is attributable to those efficacy differences (e.g increased hospitalisations) rather than to a safety issue per se.

Asenapine shows clinically important advantages over olanzapine in terms of weight gain and effects on metabolic laboratory parameters. However, it may lead to substantial weight gain, particularly in subjects who are not overweight at baseline. Furthermore, olanzapine is recognised as being particularly problematic in this regard and most atypical antipsychotics are superior to it. The profile of asenapine in terms of weight gain appears broadly similar to risperidone.

The incidence of extrapyramidal symptoms (EPS) in subjects treated with asenapine at therapeutic doses (5-10mg BID) was slightly higher than in the risperidone or olanzapine groups. All of the atypical antipsychotics studied produced substantially less EPS than haloperidol which is to be expected.

Dry mouth was reported for asenapine (2.6%) but less frequently than for olanzapine (8%).

For prolactin there was no clear difference from olanzapine but asenapine caused significantly less elevation of prolactin levels than risperidone and haloperidol.

Asenapine seemed to be benign in terms of QT prolongation which is an advantage over sertindole and ziprasidone.

- Uncertainty in the knowledge about the unfavourable effects

The safety profile is generally in line with that known for this class of drug. Further data are required from the risk management programme to characterise less common undesirable effects but no substantial issues are identified at the present time.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Atypical antipsychotics have an important role in treating very serious psychiatric illnesses but also have substantial potential to cause harm. The various products differ from each other to varying degrees in their safety and efficacy profiles. Certain products, including clozapine and probably olanzapine, are more efficacious than others but the additional efficacy comes at the cost of additional safety problems. The choice of a particular atypical antipsychotic therefore needs to be tailored to the requirements of the individual patient. A new atypical antipsychotic may have a positive risk-benefit if it has safety and/or tolerability advantages over other available agents, even if there is a disadvantage in terms of efficacy. In this case the value of the safety advantage needs to be weighed against the cost in terms of lost efficacy.

- Benefit-risk balance

SCHIZOPHRENIA

The evidence from the phase 3 short term studies is weak, with inconsistent results and questionable clinical relevance. Only 1 out of 5 comparisons to placebo achieved statistical significance. In the numerous comparisons between olanzapine and asenapine the efficacy of sublingual asenapine appeared consistently to be inferior to that of olanzapine although this is probably also true for most other antipsychotics (and olanzapine has important disadvantages in terms of safety and tolerability profiles). In a meta-analysis of the three pivotal phase 3 trials the overall treatment effect of -2.7 points difference from placebo was statistically significant, but at a level that falls short of compelling (p=0.021; 95% CI -5.0 to -0.4). The lower confidence limit was not far from zero. This level of evidence from the meta-analysis is considered not extreme enough to be convincing. Adding in the phase 2 data did improve the result, with the lower bound improving to -1.5 and the p-value becoming p=0.0011. But as this combined the hypothesis generating and the pivotal data there is a higher hurdle to meet. Ideally the phase 3 data alone should provide compelling evidence of efficacy.

The meta-analysis of PANSS 30% responders did not seem to greatly strengthen the equivocal findings on the primary endpoint. The confidence interval for the phase III meta-analysis for the difference between treatments did not exclude zero, though the trend favoured asenapine. Even if the phase II study 041004 is added in the lower bound is only 0.1%.

The clinical significance of the difference from placebo in mean PANSS score remains doubtful. The mean treatment effect seen for Sycrest of 2.7 points on the PANSS (3.7 if the phase 2 study 041004 is included) was substantially less than the comparable results from the phase 3 trials for currently approved products. The responder analyses for the combined Phase 3 population were also unconvincing.

There was a total absence of clinical evidence that the proposed upper dose of 10mg is superior to 5mg; indeed the trends tend to favour 5mg over 10mg.

Asenapine was shown to be inferior to Olanzapine in the long-term trial 25517. As the trial did not include a placebo group it cannot provide any evidence of efficacy.

In the relapse prevention trial A7501012 there was a statistically significant benefit for staying with asenapine compared to staying on placebo ($p<0.001$ on log-rank test). If short term benefit can be established this would provide support for long-term treatment, but as short-term benefit has not been

demonstrated the study is of limited relevance. The extensions to the phase III short-term trials lacked the power to draw any conclusions on the comparative efficacy of the two treatments and the lack of a placebo control in Negative Symptoms trial 25543 meant that it could not provide evidence of efficacy.

In conclusion there is insufficient evidence of short term efficacy to support the schizophrenia indication.

Given that the overall safety profile appeared comparable to other approved antipsychotics in this indication, the benefit-risk balance for asenapine is negative.

BIPOLAR I DISORDER

The efficacy in reducing manic symptoms over 3 weeks was demonstrated. However, the clinical significance of the treatment effect of Sycrest in the short term studies A7501004 and A7501005 appeared modest (especially in the former) and Sycrest appeared to have inferior efficacy to Olanzapine. In the company's responses the size of the treatment effect was shown to be in line with responses seen for other approved atypical antipsychotics, and the results were also comparable to those from the phase 3 pivotal trials supporting the marketing authorisation applications for other atypical antipsychotics. The fact that olanzapine seemed to show greater efficacy is not a barrier to approval as olanzapine probably has greater efficacy than a number of atypical antipsychotics

approved for the treatment of bipolar I disorder but also has major safety and tolerability disadvantages.

Maintenance of effect during the episode has been demonstrated. The original analysis of A7501006 was inadequate as it did not represent a comparison of randomised groups. In the re-presentation of the 12-week data accounting for all randomised patients, non-inferiority to olanzapine was not formally shown. It is not considered a requirement to achieve this as olanzapine probably has superior efficacy to most other atypical antipsychotics. Superiority to a putative placebo was shown indirectly but reasonably convincingly and this is considered sufficient. Maintenance of effect is therefore considered to be adequately shown.

The benefit of combination treatment with a mood-stabiliser has been sufficiently established.

The efficacy for asenapine can be considered to be adequately demonstrated as a treatment for Bipolar I disorder.

The overall safety profile appeared comparable to other approved antipsychotics in this indication.

In conclusion, the benefit-risk balance for asenapine is positive.

However, the optimal dosing regimen has not been established as no dose finding studies have been conducted. The company has provided a commitment to perform a dose finding study as a post-approval commitment.

- Discussion on the benefit-risk balance

SCHIZOPHRENIA

The CHMP considered the risk-benefit of asenapine in "the treatment of schizophrenia in adults" is negative for the following reasons:

- There is insufficient evidence of efficacy from short term trials.

- The magnitude of the claimed efficacy is of doubtful clinical significance.

- In the absence of adequate evidence of efficacy from short term trials, the long term trials cannot provide meaningful evidence of efficacy.

- The long term comparison to olanzapine did not provide evidence of efficacy.

BIPOLAR I DISORDER

The CHMP considered the risk-benefit of asenapine is positive, provided the indication is as follows: "treatment of moderate to severe manic episodes associated with bipolar I disorder in adults". A dose finding study will be carried out by the applicant as part of post-approval commitment.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Sycrest in the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults was favourable and therefore recommended the granting of the marketing authorisation.

Votrient

Risk-benefit assessment

Pazopanib has been shown to be an effective drug for patients with advanced renal cell carcinoma, both naïve and cytokine-pretreated. The difference in median PFS of about 5 months compared to placebo was found statistically significant and it is considered clinically relevant. The choice of placebo as comparator in the pivotal trial was an initial concern supported by two centralised scientific advices (initial and clarification) given by the CHMP recommending the conduction of a study with an active comparator. Although cytokine-based therapy (IFN-α, IL-2) was generally accepted as the treatment of choice at the time this trial was initiated, the CHMP acknowledged that cytokine-based therapy was not considered the standard of care in many countries due to its limited efficacy and excessive toxicity. At the time of submission of this application however, several new therapies were available for patients with advanced RCC (including the anti-VEGF antibody bevacizumab, tyrosine kinase inhibitors such as sorafenib and sunitinib, and mTOR inhibitors such as temsirolimus and everolimus). Therefore, the CHMP was of the opinion that even though in the specific case of pazopanib it has been shown that the product is effective, an active comparator with other TKI inhibitors was necessary in order to rule out that the use of pazopanib would mean a loss of opportunity for the patients. Analysis of historical data including a qualitative comparison and discussion of biases has been provided by the applicant, however the data itself were not considered to provide conclusive evidence.

The safety profile of pazopanib was overall similar to other marketed TKIs and inhibitors of angiogenesis and a consistent pattern was demonstrated across all RCC studies. Most of the toxicities are manageable including diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase and abdominal pain as the most frequent, but serious and potentially fatal SAEs can occur (transient ischaemic attack, ischaemic stroke, myocardial ischaemia, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage). Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke. In conclusion, no new safety concerns have been identified, however of particular importance is the fact that pazopanib inhibits the same targets as other TKIs with a different potency and selectivity leading to differences in the safety profiles.

As per CHMP request, an oncology Scientific Advisory Group (SAG) meeting was convened on 8 January 2010 to discuss the benefits/risks of pazopanib from a clinical perspective and whether it was possible to rule out with reasonable certainty that pazopanib could be associated with the risk of a clinically relevant loss in terms of efficacy or safety compared to currently approved agents in this indication. The SAG provided advice on the following questions raised by the Committee:

1. Please discuss from a clinical perspective the benefit and risk of pazopanib in advanced RCC on the basis of the Rapporteurs' reports and the data presented by the applicant (pivotal study VEG105192).

The SAG unanimously agreed that from a clinical perspective the benefits particularly in terms of PFS as observed from the main results of the pivotal Phase III Study VEG105192 compared favorably

against the toxicity, which was considered as generally manageable and overall acceptable compared to the benefits. It is important to note that the data presented refer to patients who have had no or only cytokinebased treatment for advanced RCC. There are no comprehensive data on the benefits and risks of pazopanib in patients who have previously received systemic treatments other than with cytokines. In the absence of relevant data, no benefit-risk assessment for pazopanib can be made for patients pretreated with other systemic treatments (including TKI inhibitors, mTOR inhibitors or a combination of cytokines and anti-VEGF).

2. Please discuss how appropriate choice of therapy can be made in clinical practice in the light of the current data about efficacy and safety of pazopanib and the currently approved agents. Is further information needed in order to make an appropriate choice of therapy?

Currently, there are no direct comparative data to allow an accurate estimation of the differences between available treatments for first-line treatment of advanced RCC. In the absence of direct comparative data, indirect comparisons based in particular on the individual safety profiles can guide the clinical choice among different agents that have shown a high activity in this setting. Based on indirect comparisons, there are some events that occur with a higher frequency for the approved agents (rash, mucositis, HFS) while others occur with a higher frequency with pazopanib (high grade ALT elevations, all-grade hypertension and hair discoloration). There may be other factors such as route of administration and other preferences that will play a role. Although this should not be a prerequisite for approval, it is important that comparative studies are conducted, and that these are adequately powered to detect small differences (in either direction) in terms of efficacy, and that they allow a thorough exploration of any important differences in terms of toxicity. It should be assessed if the ongoing comparative study of pazopanib versus sunitinib fulfills these requirements. Although this was not extensively presented, a non-inferiority design and a delta of >2 months difference in median PFS may not be the ideal design to detect small treatment differences. The statistical considerations, including power, sample size and design of this study should be carefully assessed.

3. Please discuss the relevance and acceptability of the applicant's inter-trial comparison for the assessment of the benefit and risk of pazopanib in advanced RCC as compared to other TKIs.

The inter-trial comparisons presented are relevant and useful to put the data into a clinical and historical perspective. However, it is impossible to draw any firm conclusions because the historical comparison includes studies with different populations, prognosis, etc.

4. With the available information about pazopanib and the currently approved agents, is it possible to rule out with reasonable certainty a risk of clinically relevant loss in terms of efficacy or safety when using pazopanib in the claimed indication compared to currently approved agents in this indication? What is the strength of evidence for the conclusions? What would be the magnitude of such loss?

The SAG agreed that a major loss in efficacy (e.g., several months of difference in median PFS or OS) or safety appears unlikely to be associated to pazopanib compared to other available treatment options. The basis of evidence for this assumption is the clear benefit of pazopanib and acceptable toxicity as observed in a well-conducted randomised controlled trial against placebo, as well as indirect comparisons and expert clinical judgement. However, the available data do not allow drawing any firm conclusions. An adequately powered study should be conducted post-approval to formally assess any differences in efficacy and allow a thorough exploration of important differences in toxicity (see also answer to Question 2). According to some members, the clinical documentation was not considered to be comprehensive in the absence of an active-controlled study, and argued that this study was considered essential to confirm the benefit-risk balance and should be conducted as part of a specific obligation in a conditional marketing authorisation.

The CHMP considered the data submitted by the applicant and the argumentation put forward by the applicant and the SAG experts. The CHMP considered that the benefit-risk balance for pazopanib was positive. There is a need however to obtain further data of the efficacy and safety in the context of an adequate active comparator to allow an accurate estimation of the differences between available treatments. The CHMP acknowledged that the pivotal trial was at a very advanced stage at the time when other TKI therapies were approved and that the trial was started at a time when useful comparators were not available. Thus, the CHMP proposed a conditional marketing authorisation, after having consulted the applicant. The CHMP considered that pazopanib is an orphan medicinal product which aims at the treatment of a life-threatening disease, and therefore falls within the scope of Regulation (EC) No 507/2006.

In connection with the review of the orphan designation criteria by the Committee on Orphan Medicinal Products (COMP) at its meeting of 7-8 April 2010, the Applicant requested the Commission to remove the product from the Community Register of Orphan Medicinal Products on 7 April 2010. As a consequence, the CHMP considered at its April CHMP meeting that Votrient still falls within the scope of Regulation (EC) No 507/2006, i.e. under Article 2(1) – medicinal product which aims at the treatment, he prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases and issued a revised opinion recommending the granting of conditional Marketing authorisation.

In addition the CHMP considered that pazopanib fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

a) Efficacy in terms of PFS prolongation has been demonstrated in a pivotal Phase III, randomized, duble-blind, placebo-controlled multi-centre study conducted in advanced renal cell carcinoma patients. Overall, a delay of the median time to progression of about 5 months was observed. A favourable effect of pazopanib was also observed in terms of secondary endpoints including overall response rate and duration of response. Treatment with pazopanib was associated with manageable toxicity including diarrhoea, hair colour change, hypertension, nausea, fatigue, anorexia, vomiting, dysgeusia, elevated alanine aminotransferase and elevated aspartate aminotransferase and abdominal pain. These concerns do not constitute blocking issues for an anti-cancer compound in this indication. Therefore, the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

b) There is a need to gain more understanding about the benefit-risk profile of pazopanib in the context of other available medicinal products for the same indication. In this regard the applicant has already initiated a non-inferiority Phase III randomised, controlled clinical study to evaluate the efficacy and safety of pazopanib versus the tyrosine kinase inhibibor sunitinib. The applicant has agreed to perform a pooled analysis of data from study VEG108844 and study VEG113078 (a study to evaluate efficacy and safety of pazopanib versus sunitinib for the treatment of Asian subjects with locally advanced and/or metastatic renal cell carcinoma - a sub study of VEG108844) in order to provide robust clinical data to compare the efficacy and safety of pazopanib versus sunitinib. The studies will be appropriately powered to demonstrate non-inferiority with a margin of 1.22 and a discussion on the applicability of the efficacy data from VEG113078 to the European population will provided. Thus, it is likely that the applicant will be in a position to provide the comprehensive clinical data.

c) Despite other agents that have shown relevant clinical efficacy in this setting, such as different regimens of cytokines, combination treatment with interferon alfa-2a and the anti-VEGF antibody bevacizumab, tyrosine kinase inhibitors such as sorafenib and sunitinib, and mTOR inhibitors such as temsirolimus and everolimus, there remains a large unmet medical need in the treatment of this condition because the disease eventually progresses in most patients and available treatments are associated with clinically important adverse drug reactions. Thus, different agents through different

safety and efficacy profiles may offer major therapeutic advantages to those affected in terms of clinical efficacy, safety or other aspects such as patient preference. Pazopanib has been associated with high tumour response rate and important improvement in terms of PFS in treatment naïve patients with advanced RCC and in patients with advanced RCC who were refractory to prior cytokine therapy based on a randomized controlled trial. The safety profile has been well-characterized and is considered manageable. Based on indirect comparisons, there are some events that appear to occur with a higher frequency for the approved agents (rash, mucositis, HFS) while others occur with a higher frequency with pazopanib (high grade ALT elevations, all-grade hypertension and hair discoloration). Furthermore, compared to other agents that have shown activity in advanced RCC, pazopanib has a distinct pharmacodynamic profile in terms of potency in inhibiting the main receptor tyrosine kinases involved in angiogenesis. The different pharmacodynamic profile may explain the potential differences observed in the indirect comparisons presented, although this would have to be confirmed in adequately powered randomized controlled trials. The addition of a safe treatment option that is associated with clear clinical benefits and with a distinct pharmacodynamic profile is considered to offer major advantage in the context of the therapies for this disease. Therefore the CHMP considers that unmet medical needs will be fulfilled for the treatment of advanced RCC.

d) In view of the favourable benefit-risk profile, the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required. A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by a majority decision that the risk-benefit balance of Votrient in the first line treatment of advanced Renal Cell Carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease was favourable and therefore recommended the granting of the conditional marketing authorisation. In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Votrient not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Nexavar (sorafenib), Torisel (temsirolimus) and Afinitor (everolimus) for the same therapeutic indication.

VPRIV

Benefits

- Beneficial effects

There is a considerable degree of variability in the clinical signs and symptoms of Gaucher disease, ranging from severely affected infants to asymptomatic adults. Type 1 Gaucher disease is the most common subtype; patients display a wide range of symptoms. The clinical features of type 1 Gaucher disease are dominated by accumulation of Gaucher cells in target organs liver, spleen, and bone marrow and thus include anaemia and thrombocytopenia due to splenic sequestration and bone marrow replacement, as well as splenomegaly and hepatomegaly. Besides symptomatic treatment, the goal of therapies is to reduce storage of GlcCer in affected tissues of GD patients leading to improvements in haemoglobin concentration (Hgb) and platelet count and reductions in spleen and liver volumes. The main endpoints of interest to assess the efficacy of treatments for type 1 Gaucher disease patients in clinical trials are changes in Hgb concentration, platelet count, and liver and spleen

volume, since based on the literature, haematological and visceral disease therapeutic goals can generally be met more rapidly than designated goals for skeletal or pulmonary compartments.

In the pivotal trial HGT-GCB-039 effects of treatment with 60 U/kg velaglucerase alfa over 9 months were not inferior to those seen with 60 U/kg imiglucerase. Mean changes from baseline in Hgb were comparable between velaglucerase alfa and imiglucerase treatment groups and the primary endpoint of predefined non-inferiority criteria was met. For the ITT population, the mean absolute changes were 1.624 g/dL for velaglucerase alfa and 1.488 g/dL for imiglucerase. Results were consistent with the PP population. Responses were similar between treatment groups for subgroups paediatric (age 2 to 17 years), adult (age ≥18 years), gender, and splenectomy status. The secondary endpoint time to first Hgb response, defined as an increase of ≥1 g/dL from baseline, was similar between groups (log-rank p-value = 0.8965).

Regarding the secondary endpoints, the mean platelet counts increased with both treatments. At Week 41, the unadjusted mean change was 110.4 x 10^9/L in the velaglucerase alfa and 144.4 x 10^9/L in the imiglucerase group. The model-based estimated treatment difference in mean change at Week 41 was not statistically significant. The mean change in liver volume was comparable between groups and statistically not significantly different. Regarding the change in spleen volume results indicate a substantial reduction during treatment. Results are based on 7 patients per group with spleen. Effects on plasma chitotriosidase and CCL18 values were comparable between treatment groups. For adults changes in QoL measurements appear to be comparable between groups. The exploratory endpoints Hgb, platelet count, liver and spleen volume response categories showed comparable results between velaglucerase alfa and imiglucerase groups; response categories as proposed in the CHMP scientific advice were used.

Efficacy data from the supportive study TKT025 are consistent with a clinically significant positive effect of velaglucerase alfa dosed as 60 U/kg EOW on relevant markers of type 1 Gaucher disease. Effects were maintained throughout the 9 month duration of the trial.

In study TKT032, investigating two dose groups of velaglucerase alfa, 45 and 60 U/kg, effects on Hgb and platelet count were equal or greater in the 45 U/kg dose group, while the opposite was seen for effects on liver and spleen volume and time to first Hgb response, indicating an earlier response in the 60 U/kg; no formal comparison of dose groups was prespecified. However, velaglucerase alfa induced clinically relevant effects on Hgb, platelet count, and spleen and liver volumes comparable to those seen in the other clinical trials.

Overall, data from these trials support the assumption that velaglucerase alfa is effective in increasing haemoglobin concentration and platelet count as well as reducing spleen and liver volumes in type 1 Gaucher disease patients.

No clinical studies in special populations have been performed. Exploratory subgroup analyses of data from study TKT032 do not indicate differences in the response to treatment for either age or gender. The applicant did not provide analyses of efficacy data across the clinical trials. However, assessment of data from single trials indicates comparable effects of velaglucerase alfa on Hgb, platelet count and organ volumes across trials. No placebo controlled data have been provided, which is acceptable for the patient population investigated.

- Uncertainty in the knowledge about the beneficial effects

Interpretation of the results is generally limited by the low number of patients investigated and by the fact that the majority of trials have been uncontrolled, the exception being the active-controlled trial HGT-GCB-039 with only 17 patients per arm. In this trial, there were also imbalances between treatment groups that might have affected the outcome. The median baseline Hgb was 11.4 g/dL in

the velaglucerase alfa and 10.6 g/dL in the imiglucerase group. This difference between groups remained during the entire study. However, an analysis adjusting for the baseline haemoglobin concentration values confirmed the primary efficacy analysis and the baseline difference is considered to be to the disadvantage of the efficacy of velaglucerase alfa rather than imiglucerase and thus adding reassurance to the assessment of the efficacy of velaglucerase alfa. For platelet count baseline values were higher in the imiglucerase compared to the velaglucerase alfa group (181.2 vs. 161.1 x 109/L); the difference persisted at each assessment and appeared to increase in the latter half of the study. Part of the difference might be explained by the fact that all 4 children under the age of 5 years, 3 with spleen and 1 splenectomised, were randomised to imiglucerase indicating a more severe course of disease; children with more severe disease are expected to have a better response to treatment. Post hoc analyses suggest that patients in the 2 to 4 years age group have skewed the data; those three not splenectomised had large spleens and low platelet counts at baseline and appeared to have worse disease at the start of the study. There was also a considerable imbalance in mean spleen volume at baseline, but results indicate a comparable response on change in spleen volume between groups. Regarding the assessment of QoL measurements the interpretation is hampered by the insufficient data especially in children.

There are currently no final data from study TKT025EXT contributing to the efficacy evaluation of velaglucerase alfa. The preliminary data indicate that the treatment effect is maintained over an extended period of five years in spite of lowering of the dose by 50%. The applicant has committed to provide the final CSR in an acceptable timeframe after finalisation of the trial. For the two doses of imiglucerase used in study TKT032, no formal comparison has been pre-specified or provided.

Risks

- Unfavourable effects

Exposure to velaglucerase alfa is limited, but in light of the low prevalence of type 1 Gaucher disease, considered adequate. The most relevant safety data are derived from study HGT-GCB-039; safety evaluation in this trial is limited to the 17 patients per group enrolled.

In study HGT-GCB-039 the overall AE profile appears to be comparable between treatment groups. No deaths were reported for either group during the study. SAE occurred only in patients treated with velaglucerase alfa, but only 1 of the 4 SAE, an allergic skin reaction, is considered probably treatment related. Since allergic skin reactions have also been described for imiglucerase, the difference is most likely a chance finding due to the low number of patients treated per group.

One case of prolonged aPTT occurred in the velaglucerase alfa group compared to none in the imiglucerase group. The event is adequately reflected in the SmPC.

No patient on velaglucerase alfa developed anti-velaglucerase alfa antibodies throughout the study compared to 4 on imiglucerase. However, infusion related AEs were balanced between groups. Overall laboratory findings do not indicate significant differences between treatment groups.

Regarding safety in special populations subgroup analyses have been provided for age, gender, and splenectomy status. Overall AE profiles are considered comparable between age groups, female and male patients, and patients with and without spleen. There are no safety signals specific to the paediatric population.

No data on drug-drug or drug-disease interactions with regard to safety have been provided. There were no relevant differences in discontinuation due to AEs between treatment groups and compliance was high in both groups.

For the overall data set there have been no unexpected findings in the analyses of SAEs and deaths; no death occurred during the trials.

Six patients on velaglucerase alfa compared to none on imiglucerase developed a prolonged aPTT. Although these events appear to be related to the underlying disease rather than being a treatment effect the limited data do not allow a definite conclusion and thus prolonged aPTT is considered a potential risk to be included in the RMP. The event is however appropriately reflected in the SPC.

Antibody formation appears to be numerically higher in patients on imiglucerase than on velaglucerase alfa, but absolute numbers are low and thus no definite conclusion is possible.

In the subgroup analyses of AE for age and gender, findings do not indicate differences in the AE profiles.

Infusion related AEs occurred with velaglucerase alfa treatment. No unexpected findings have been reported.

Safety related to drug-drug interactions and other interactions has not been provided which is considered acceptable.

Analyses of discontinuations due to AEs do not reveal any unexpected findings.

- Uncertainty in the knowledge about the unfavourable effects

Evaluation of unfavourable effects is restricted by the limited data available. However, a planned register, called Gaucher disease Observational Survey (GOS), will collect additional data on treatment with velaglucerase alfa.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Changes in haemoglobin, platelet count, and organ volumes are considered relevant and sufficiently sensitive endpoints for the assessment of treatment efficacy. These endpoints contribute considerably to the disease burden and thus improvement in these parameters is expected to alleviate disease burden in patients with type 1 Gaucher disease. According to the literature these therapeutic goals can generally be met more rapidly than designated goals for skeletal or pulmonary compartments.

Except for the unexpected findings, antibody formation and infusion related events are considered the most relevant unfavourable effects for assessment of safety comparability between ERT groups. Antibody formation might reduce efficacy, as well as it might lead to infusion-related events. Infusion-related events might either jeopardise compliance or even render treatment impossible due to severe anaphylactic reactions.

- Benefit-risk balance

Treatment of type 1 Gaucher disease patients with velaglucerase alfa leads to significant and clinically relevant improvements in haemoglobin concentration, platelet count, and spleen and liver organ volumes. These changes are sustained throughout the studies. The observed changes are considered comparable to those seen with the established ERT imiglucerase.

No unexpected safety findings except a prolongation of aPTT have been identified. Thus the data provided indicate that the benefits seen with velaglucerase alfa treatment outweigh the risks involved with this treatment and that the benefit-risk balance is comparable to that for the established ERT with imiglucerase. Thus, the benefit/risk balance is positive.

- Discussion on the benefit-risk balance

Efficacy data from trial HGT-GCB-039 indicate that velaglucerase alfa 60 U/kg EOW in treatment naïve patients is not inferior to the currently licensed imiglucerase as assessed by increases in Hgb and platelet count and decreases in liver and spleen volumes. Data from supportive studies are in line with the findings in this pivotal trial. Patients transitioned from imiglucerase to velaglucerase alfa showed sustained clinical effects in Hgb and platelet count. Long term data do not indicate any inconsistent effects in increases in Hgb and platelet count, or decreases in liver and spleen volumes. Efficacy results were consistent between paediatric and adult patients and no gender related differences were seen. The adverse event profile is considered comparable to that of imiglucerase. Thus in consequence it is considered that the benefit outweighs potential risks with velaglucerase alfa treatment.

The absence of data from placebo-controlled trials is acceptable, placebo-controlled trials are not considered feasible in the patient population investigated due to ethical concerns.

In conclusion, the safety data provided do not indicate significant differences in safety between velaglucerase alfa and imiglucerase. Besides the prolonged aPTT, no unexpected safety findings have been identified during the trials conducted with velaglucerase alfa. Nevertheless the evaluation is limited by the low number of patients exposed to velaglucerase alfa in these trials. This should be adequately considered in the Risk Management Plan.

Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Additional pharmacovigilance planning was needed to adequately monitor the safety of the product.
- No additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of VPRIV in the treatment of patients with type 1 Gaucher disease was favourable and therefore recommended the granting of the marketing authorisation.

and

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers VPRIV not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Zavesca for the same therapeutic indication.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not completed yet as none of the measures are completed.

2. Benefit Risk assessments - from the EPAR of new active substance applications" with negative outcomes in 2010. (As available on 07 February 2011)

- **Cerepro** had a negative CHMP opinion in 2009, which was subject to a re-examination by the CHMP. However the company withdrew the application during this procedure in 2010. The details of the CHMP concerns can be formulated as "-The efficacy data submitted do not demonstrate the benefit of Cerepro in the claimed indication. The primary efficacy analysis did not show any statistically and clinically significant difference between the active treatment and the control arm; in this failed trial any post-hoc subgroup analyses can only be considered as exploratory.-In addition, during this open label trial, the company changed the primary endpoint in a sequential design from 'overall survival' to "time to death or re-intervention", which is prone to bias by treating physicians.-The administration of Cerepro is associated with an increased incidence of adverse events and of serious adverse events (e.g. hemiparesis, seizures). In view of the lack of proven efficacy of Cerepro and the risk management submitted, the documented side effects result in a negative benefit/risk ratio".
- **Comfyde.** The company withdrew the application prior to receipt of the CHMP list of question. As the CHMP was evaluating the initial documentation provided by the company, it had not yet made any recommendations
- **Joulferon.** The company withdrew the application prior to receipt of the CHMP list of question
- **Zeftera** had a majority negative CHMP opinion. The grounds for the refusal were formulated as follows. "Whereas •The pivotal clinical studies BAP00154 and BAP00414 were not conducted in accordance with GCP as required by Annex I of Directive 2001/83/EC as amended and the nature of the findings is such that the conduct of the studies and their results cannot be relied on to recommend the granting of a marketing authorisation. •The therapeutic efficacy and clinical safety have been insufficiently substantiated by the applicant as per article 12(2) of Regulation (EC) No 726/2004 and article 26(1)(b) of Directive 2001/83/EC as amended. •The risk/benefit balance is not considered to be favourable as per article 26(1)(a) of Directive 2001/83/EC as amended".

  Some members had a divergent view and considered that there was "sufficient evidence to support the overall reliability of the data and the positive benefit risk balance of the antibiotic, especially given the need for new antimicrobial agents".
- **Zenhale.** The company withdrew the application before the final CHMP opinion. The following information has been published on the EMA website: "Based on the review of the data and the company's response to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Zenhale could not have been approved for the maintenance treatment of asthma.

  Following a routine inspection of study sites, the CHMP had concerns over the way the studies were conducted in some sites, which cast doubt on the reliability of the results. The CHMP also had concerns with one of the comparator medicines, mometasone furoate, which was not in an approved formulation. The company was asked to provide further data to justify the use of that comparator, specifically to show how mometasone furoate in the comparator was released in the body compared with the approved mometasone furoate.

3. Benefit Risk assessments - from the EPAR of extensions of indications in 2010. (As available on 07 February 2011).

Anti-infectives and vaccines

Gardasil (human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed)), to include the prevention of premalignant genital lesions, cervical cancer and external genital warts in mid-adult women, from the age of 26 to 45 years.

Benefit-risk assessment

The results at end of study confirmed and extended the efficacy of the qHPV vaccine in MAW demonstrated in the 2007 endpoint driven analysis. The qHPV vaccine was highly efficacious in the PPE population with respect to the relevant endpoints, persistent infection, CIN and EGL. High efficacy was observed with respect to HPV 16 and HPV 18 individually, with respect to persistent infection alone and with respect to disease endpoints (CIN, AIS, or EGL) alone. There were no new cases of HPV 6/11/16/18-related CIN or EGL reported in the qHPV group since the first analysis. Hence, the results in study 019 showed significant vaccine efficacy in HPV naïve MAW and in similar magnitude as that shown in YAW. In the FAS population improved efficacy results were demonstrated during the additional 2-year follow-up. The efficacy estimates against HPV 16/18-related PI/disease endpoint now reached statistical significance. There were a total of 48 (qHPV=21, placebo =27) cases of vaccine type related CIN 2/3 in the FAS population with no new cases in the vaccine group since the first analysis. The issues raised during the previous regulatory procedure, which included efficacy against HPV 16/18-related persistent infection by duration of infection (6 or 12 months), relevance of the HPV 6/11-related persistent infection endpoint, poor vaccine efficacy in the FAS population, delayed clearance of HPV 16 infection in the Day 1 PCR positive and seronegative population of the vaccine group, and the potential of vaccine-induced acceleration of disease and of replacement by non-vaccine types, were properly addressed.

The vaccine-induced immune responses in MAW were robust, but lower than those observed in younger 16- to 23- year-old women. The consequence of these lower antibody responses in MAW for long-term efficacy is not known since no minimum anti-HPV level that confers protection has been defined. The low persistence of GMTs and seropositivity for HPV 18 at end-of-study did not translate into loss of efficacy, but need to be closely monitored in the future. The MAH has already committed to conduct a 10-year follow-up of Protocol 019 in Columbia to evaluate long term immunogenicity and efficacy in mid-adult women, which is satisfactory. The MAH has also already committed to apply broader neutralization assays to further characterize the vaccine induced immune responses (see letter of undertaking).

Administration of qHPV vaccine is generally well tolerated in 24- to 45-year-old women. The present safety data support the conclusion that qHPV vaccine is well tolerated and displays a safety profile similar to that shown in previous submissions. No safety signals have been identified with the exception of increased incidences of transient injection-site adverse experiences and low-grade fever following vaccination. There were no new vaccine-related serious adverse experiences in the present report. Additionally the MAH committed to update the CHMP with regard to the feasibility of extending to 45 years of age the ongoing PGRx studies (see letter of undertaking).

The revised RMP version 4 in relation to the extension of the indication to mid-adult women has been adequately updated, including a commitment to perform a long-term observational study on viral type replacement, long-term effectiveness/immunogenicity and long-term safety in Columbia (see letter of

undertaking). The assessment of the outline of the study protocol is on going. Annex II was updated with the revised version of the RMP.

The overall expected benefit of the qHPV vaccine in mid-adult women is lower than in the young adult women population, due to the higher level of baseline sero-/PCR-positivity and the much lower risk of acquiring of new HPV infection at older ages. However, based on the result in Protocol 019 it is evident that efficacy in HPV naïve older women is of the same magnitude as that in young adult women. Since the overall expected benefit of the qHPV vaccine in mid-adult women is lower than in the young adult women population the CHMP considered important to alert the prescribers that HPV exposure and potential benefit should be considered in the decision to vaccinate an individual adult women. Further important information for prescribers already mentioned in the product information include statements that the vaccine does not protect against all HPV types and therefore it is critical that the women continue to attend routine cervical screening according to local recommendations and that Gardasil is for prophylactic use only and has no effect on active HPV infections or established clinical disease.

The product information was updated to reflect these data as detailed in section 3.7 and the above mentioned commitments were included in the letter of undertaking.

Reyataz (atazanavir), to extend the therapeutic indication to include the treatment of HIV-1 infected paediatric patients above 6 years of age.

Benefit-risk assessment

Reyataz (atazanavir) is currently only indicated in HIV infected adults in combination with other antiretroviral medicinal products. Atazanavir has pharmacokinetics that allow once daily dosing in adults, which makes a paediatric development program desirable as adherence could be expected to improve with such a regimen in this population. Also, the introduction of a formulation allowing use in small children would be desirable.

The clinical development of antiretrovirals in children should focus on the dose selection. Its purpose is not the duplication of the clinical efficacy and safety demonstration obtained in adult patients. The selected dose should achieve comparable exposures in children as those observed in adults. Based on the underlying rational that this will lead to a comparable efficacy and safety profile of the medicine, no further clinical data would be required to support a positive benefit risk balance in this population. However, during the initial evaluation, it was concluded that the dose selection of atazanavir boosted with ritonavir in the MAH's claimed paediatric indication, i.e. in children above 3 months of age, was far from being adequately substantiated by the MAH in support of the claimed extension of indication in children. Indeed, both the clinical study (AI424020/PACTG1020A) and the PPK analysis that supported the indication suffered from critical deficiencies. As a consequence a major objection was raised by the CHMP.

The followings issues have been addressed by the MAH within the submitted responses.

The main concern was a greater peak-to-trough ratio in children as compared to adult patients. From the data provided by the MAH, it was confirmed that mean C_{max} values were higher, whereas mean C_{min} values were lower in younger patients compared to older patients. However, mean AUC values were similar for patients in the whole age range from 6 to 13 years. Overall, it is clear that a greater peak-to-trough ratio was mainly observed in the youngest children and that in patients aged 6 years and older, this concern was quite alleviated with a significant less higher peak-to-trough ratio.

In response to the CHMP concern the MAH has only retained the limit of 6 years of age in its revised claim for the paediatric extension. Nonetheless the CHMP agreed with this proposal given the limitation

of the data in younger children. The MAH is still encouraged to adequately develop the medicine in younger children than 6 years of age to answer a medical need.

Another concern raised was the absence of clinical data to substantiate the BW-based dosing recommended regimen, since only BSA-based doses were investigated in the clinical study. In responses to this concern, the MAH provided data comparing the proposed BW-based (derived from the modelling/simulation) to the BSA-based doses (administered in the clinical study). Based on these data the BW-based dosing can be accepted, all the more that it is more convenient in clinical practice.

As expected based on the clinical experience in adults, a much better response rate is obtained in antiretroviral naïve than in experienced children. This further illustrates the limitations of atazanavir/RTV to be used in moderately experienced patients. The benefit/risk of atazanavir/RTV in antiretroviral experienced paediatric patients was extensively discussed. Due to the very limited number of antiretroviral experienced children no clinical cut off could be determined in these patients.

The indication was granted to allow the use of this boosted PI in some ARV experienced children (e.g. in children having stopped their boosted PI for intolerance or poor adherence, before having accumulated multiple PI resistance). However, strong warnings were included to make prescribers aware of the limitations of the data and results in experienced patients: "Atazanavir/ritonavir is not effective in viral strains harbouring multiple mutations of resistance. While in adults no benefit can be expected in patients with ε4 PI mutations, in treatment experienced children even lower numbers of PI mutations may be predictive of a lack of benefit."

It is worth noting that when focusing on the target population of the claimed indication, i.e. children aged 6-18 years, it only consists of 16 antiretroviral naïve patients and 25 antiretroviral experienced patients (please see discussion above). The indication was revised to highlight this limited amount of data. Even if it is acknowledged that it is not so far from the limitation of the database for other boosted PIs in paediatric patients, this is nevertheless very limited and requires reinforced postmarketing surveillance in this population (through the RMP). The MAH committed to submit a protocol for its involvement with the PENTA foundation cohorts to follow the paediatric population.

Based on the clinical experience gained in adults, hyperbilirubinemia represents the most salient aspect of the safety profile of atazanavir. As in adults, hyperbilirubinemia accounts for the most frequent serious adverse event observed in children. Nevertheless, it is admitted that hyperbilirubinemia, although frequent, is a manageable adverse event and does not give rise to serious safety concerns. Of note, this nevertheless may have some potential psychosocial impact in the adolescent population.

In addition to that, it is important to have a particular focus to the cardiotoxicity findings in the paediatric study submitted.

Forty-four (44) paediatric patients (24%) presented an AV block in this study, 26 treated with ATV alone (31%) and 18 treated with ATV/RTV (19%). This appears to be more frequent than in adults. The higher percent of AV block in patients treated with unboosted ATV was in line with the higher total daily doses and C_{max} observed in this group compared to RTV-boosted ATV. The safety data observed in the current paediatric study confirmed the previously observed safety data in adults (prolongations in PR interval and occurrence of AV block in patients treated by ATV). These adverse events are dosedependent.

This cardiotoxicity although even observed in adults may raise some specific concerns for the paediatric population insofar that

- children are expected to present higher C_{max} values than adults

- given that cardiotoxicity management is more likely required in the adult population than in paediatric population, performing a cardiac monitoring (outside specialised units) may result to be more complex in children in clinical practice than in adults.

Therefore, sections 4.4 and 4.8 of the SmPC were revised to give a clear message as regards the precaution to be taken before and during the treatment by atazanavir/RTV in children.

Viread (tenofovir disoproxil), to include treatment of chronic hepatitis B in adults with decompensated liver disease.

Benefit-risk assessment

The MA of Viread was first granted for the treatment of HIV infection and more recently for the treatment of chronic HBV infection in patients with compensated liver disease. The MAH now applies for an extension of indication for the treatment of patients with chronic HBV infection and decompensated liver disease.

In support to this claim the MAH has submitted a Phase 2, Double-Blind, Multi-centre, randomised Study. This is a three arms study with two monotherapy arms: Tenofovir Disoproxil Fumarate, and Entecavir and a third arm with the fixed dose combination of Emtricitabine Plus Tenofovir Disoproxil Fumarate.

This study is ongoing with a 168 weeks follow-up. The 48 weeks data have been submitted.

Tenofovir and entecavir, due to their potent virologic activity and high genetic barrier, nowadays supersede existing therapeutic options. Despite not being granted any MA for the treatment of decompensated patients, they are already recommended in the therapeutic guidelines.

This study is mainly aimed at responding to the need for safety data for tenofovir in decompensated patients. The primary endpoint then relies on safety. Morever, this study is to be regarded as "confirmatory" for the efficacy as well.

The study comprises two coprimary safety endpoints (subject discontinuations due to tolerability failure and confirmed ≥ 0.5 mg/dL increase in serum creatinine or decrease in serum phosphorus to < 2.0 mg/dL).

As regards the efficacy results an undetectable viral load (LOQ 400 copies/ml) is achieved for around 70% of patients receiving the monotherapy with either tenofovir or entecavir.

A marked trend (>15%) for higher response rate was observed in the FTC/TDF arm (which might even be underestimated, given the trend for more severe patients at baseline in the combination arm). This virological difference is parallel with the proportion of patients with ALT normalization (around 20%). However, this study was not designed to compare Viread and Truvada efficacy. Even though the data are suggestive of a superiority of Truvada over Viread the data derived from this study are too limited to enable reliable comparison between these drugs. The MAH was further requested to address this issue and committed to discuss the possibility of demonstrating the superiority of Truvada versus Viread in the therapeutic management of patients with decompensated liver disease (see letter of undertaking).

As regards safety results patients with decompensated liver disease are expected to be at higher risk of experiencing renal disorders, which is the key safety aspect profile of TDF. A slightly higher proportion of subjects with confirmed renal laboratory abnormalities were reported in patients with hepatic decompensation. In all reported cases, renal impairment was related to the progression of the

underlying liver disease rather than a direct toxicity of the drug. No marked difference was seen regarding this issue between the three treatment arms.

Based on the final 48 week results from study 0108, the safety profile of TDF appears globally acceptable in subjects with liver decompensation and consistent with what expected in this population of patients characterised by a greater severity of the liver disease. The safety profile of Viread in HBV patients with decompensated liver disease does not appear markedly different from the safety profile in HBV patients with compensated liver disease. No new safety concern has emerged.

However, the degree of reassurance on the tenofovir safety that could be derived from this study is hampered by the limited number of patients with CPT score >9. Therefore, the CHMP considered appropriate the update of the SmPC with a warning alerting prescribers that there are limited data on the safety and efficacy of tenofovir disoproxil fumarate in HBV infected patients with decompensated liver disease and who have a Child Pugh Turcotte (CPT) score > 9. These patients may be at higher risk of experiencing serious hepatic or renal adverse reactions. Therefore, hepatobiliary and renal parameters should be closely monitored in this patient population.

Combined to available resistance data for compensated hepatic patients at week 144, the resistance data for decompensated hepatic patients at 48 weeks are reassuring.

The MAH has submitted a RMP. The CHMP considered that development of resistance in HBV infected patients remains a potential risk during long term exposure. The CHMP considered that safety in patients with decompensated liver disease should be kept in the RMP as missing information until long term data is generated. Furthermore, following CHMP request the RMP was modified and limited safety data for in HBV infected patients with decompensated liver disease and CPT score >9 and routine risk minimisation activities was included as missing information in the RMP. The proposed RMP is suitable for the new indication.

Further safety data are expected from this study to substantiate the safety profile of the drug in patients with decompensated liver disease with longer treatment duration.

In conclusion based on the above data on safety and efficacy the CHMP endorsed the extension of indication to include the treatment of chronic hepatitis B in adults with decompensated liver disease.

Central Nervous System and Ophthalmology

Lucentis (ranibizumab), to include the treatment of visual impairment due to diabetic macular oedema.

Benefit-risk assessment

Benefits

The mechanism of action of ranibizumab is to decrease permeability of leaking blood vessels. This mechanism of action is valid independent on whether targeting retinal vessels in DME or choroidal vessels in AMD. Therefore, available data from the AMD-population adds to the basic understanding of the drug. This is of relevance also for understanding the treatment of DME.

A statistically convincing effect of ranibizumab in the treatment of visual impairment due to DME has been demonstrated in one phase II (RESOLVE) and one phase III study (RESTORE). Sufficient data support the choice of dose, 0.5 mg, the flexible dosing frequency, the re-treatment and stopping criteria that are based on assessment of VA. The effect of ranibizumab was consistently superior to that of sham treatment or laser photocoagulation. The effect of ranibizumab as monotherapy or if

combined with laser treatment was similar and consistent across analysis of primary and secondary analyses independent on analysis population.

In the pivotal, RESTORE study, the mean average improvement in VA (+6 letters- similar in both ranibizumab treatment arm, vs. +1 letter in the laser therapy group) as well as the proportion of subjects that gained ≥ 10 (~40%) or ≥15 (23%) letters (16 and 8 % in the laser group) in VA was lower than in RESOLVE (8 letter mean average improvement, vs. no change in the sham group, 62 and 36 % gained ≥ 10 and ≥15 letters vs. 19 and 9% in the sham group).

In ranibizumab-treated eyes, the increase in VA was rapid and continued over 6-12 months, thus the analysis of VA as an average mean over time is highly conservative. Therefore, the key secondary endpoint analysing the "mean change from baseline at 12 months", is considered of equal importance. After 12 months treatment, the mean improvement in VA was 11 letters vs. no change in the sham group (-0.4 letters) in RESOLVE and 7 (similar in both ranibizumab treatment arm) vs. 1 letter in the laser treatment arm in RESTORE.

Subjects with a lower baseline VA had the most benefit from treatment, but due to a potential ceiling effect for subjects with a better baseline VA (some subjects reached ≥84 letters, ~20/20 Snellen equivalents in VA), no overall conclusion can be drawn. Therefore, the lower overall gain in VA in RESTORE may not be surprising since the population in this study had a better baseline VA (+3 letters) and less CRT (-40μm) compared to subjects in RESOLVE. This is supported by additional analysis, although limited, on RESTORE-subjects with RESOLVE-like inclusion/exclusion criteria.

Even though the improvement in VA alone is not significant, the proportion of subjects that gain ≥10 and ≥15 letters/reach the 'ceiling' of 84 letters is considered to be of clinical relevance. The proportion of subjects that had a VA of >73 letters (~50%) or < 39 letters (1-3%) was also clinically significant and comparable to the outcome in RESOLVE. Overall, it is considered that the meaningful benefit of ranibizumab indicated from RESOLVE has been confirmed in the RESTORE study and that this effect is relevant for the majority of patients in the target population.

Many subgroups were of limited size. However, with one exception, subgroup analyses indicate a benefit of ranibizumab (±laser) over laser. The very limited subgroup of subjects with a rather good baseline VA (>73 letters, 20/40 Snellen equivalent) together with a limited DME (<300 μm) had no additional benefit of ranibizumab-treatment. The observations that the duration of DME, previous laser photocoagulation or the presence of significant retinal ischaemia did not appear to influence the effect of ranibizumab-treatment is important, both from the patient's view and from the perspective of clinical practice. Few subjects with type I diabetes were included in the two studies. In type I diabetes, vision loss is predominantly due to proliferative complications while in type II, mainly due to DME. However, in this study no subjects with proliferative retinopathy were included, only subjects with DME and DME as such should not differ between the subgroups. Furthermore, there was evidence of a treatment effect of ranibizumab also in subjects with Type I diabetes.

The presented studies are limited to 12 months and the long-term effects on VA are not known. However, the recently published study from DRCRnet (similar population as in the submitted studies) has 2-year data available from ~200 subjects treated with Lucentis and laser photocoagulation (377 such patients treated for 1 year). During the 2nd year, subjects received 2-3 additional ranibizumab-injections while essentially maintaining the 12-month gain in VA (9 letters).

Overall, from a clinical perspective, the demonstrated effect appears convincing since, even with laser treatment (the only currently available treatment) no significant improvement of VA is to be expected in this population.

- Uncertainty in the knowledge about the beneficial effects.

The persistence of the effect of ranibizumab, i.e. treatment-free intervals, of ranibizumab needs to be further explored to evaluate a more practical dosing regimen. Although treatment with ranibizumab has been the first treatment that significantly improves VA over 12 months in subjects with visual impairment due to DME, the long term effects of treatment is not known. A long treatment may be expected since the current target population is 10-15 years younger than the previously studied AMD-population. Although some support is given by the recently published DRCRnet study, additional long-term data is needed. Such data are to be generated in planned and ongoing studies.

Ranibizumab may be used as monotherapy or in combination with laser photocoagulation. However, it is not known if an early, and maybe not lasting, gain in VA due to ranibizumab-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. On the other hand, since there were no additional treatment benefits with the combination, taking the (long term) destructive effects as well as benefits of laser into account, it remains unknown which population that may have a benefit of the combination treatment and how the combination is best used.

Risks

- Demonstrated risks

Ranibizumab is given by IVT injections. The risks with such injections are characterised in the previous development programme including patients with AMD also apply to DME. The risks consist mainly of increased IOP that is, in most cases, non-serious, transient and can be managed. In addition, there are risks for intraocular inflammation, damage to intraocular tissues including increased risks for retinal tears and detachment as well as potentially sight-threatening endophthalmitis. Overall, the submitted studies indicate that the risks are fairly similar for patients with DME and no new adverse events were reported.

With regards to non-ocular AEs, as in the AMD-population, the majority were mild to moderate in severity and few were suspected to study drug and/or ocular injection. The most important adverse events in DME patients were the previously identified AEs potentially related to systemic VEGF-inhibition. Despite a significant co-morbidity associated with diabetes, the incidence of these AEs was low and not higher than reported for AMD-patients, nor were there any new non-ocular AEs besides urinary tract infection. Supportive data from four ongoing studies in DME have, so far, also not indicated any notable differences with regards to severe AEs compared to what is already known.

One death was reported in RESOLVE and 7 in RESTORE. None were considered by the investigator to be related to study treatment. However, for some of the events, a relation to a systemic VEGF-inhibition cannot be excluded. On the other hand, this is a population with major cardiovascular co-morbidities and, in the ongoing DME studies, the frequency of fatal events reported so far is similar to the one in the AMD-studies.

- Potential risks

Overall, ranibizumab has been administered to 312 patients with DME (77 subjects in RESOLVE and 235 subjects in RESTORE) which is limited. Of these, 120 have received the combination with laser. Importantly, there appeared to be no additional risks in subjects with significant retinal ischaemia. However, few subjects have been evaluated. There is also no, or limited, information on any potential risks for, amongst others, ATEs if treating subjects with proliferative diabetic retinopathy, uncontrolled disease, previous stroke or TIA. The experience in other ethnicities than Caucasians is also limited.

On the other hand, there is additional support from the ongoing studies, from published studies as well as from patients with AMD and diabetes, although the latter population is likely to have a less severe

disease. Even though the high incidence of elevated IOP and endophthalmitis observed in DME patients in RESOLVE was not supported by data from RESTORE or from diabetic patients with AMD, available data cannot conclude on the magnitude of these ocular risks, bearing in mind the possibility of an increased susceptibility towards infections in subjects with advanced disease. A continued monitoring of these risks in the target population is needed. In addition, potential risks regarding progression of diabetic retinopathy and macular ischaemia are expected to be further addressed in the ongoing as well as planned studies.

Another uncertainty is the long-term risks in the targeted DME population. Including the elderly subjects with AMD and diabetes adds to the information on age-related risk factors in the target population. On the other hand, considering that the general DME patient with the diabetes co-morbidities is younger, additional number of years with IVT treatment may be expected. Further, very few elderly subjects with DME (and potentially more severe vascular disease) have been treated. The potential long-term risks for impairment of VA due to halting or deferring laser photocoagulation are also not known. Although the longer-term data from the study from DRCRnet (2-year data from 484 patients whereof ~200 subjects treated with Lucentis ±laser photocoagulation) support the current safety profile of ranibizumab in the treatment of patients with DME, additional long-term safety data are needed. Such data are to be generated in planned and ongoing studies.

Given the IVT route of administration, a limited absorption into the systemic circulation is expected. Since subjects with DME have more permeable eyes compared to subjects with AMD, there may be an increased systemic exposure. The submitted pharmacokinetic data in this population is limited, but indicate that some subjects may have a slightly higher maximal plasma exposure level than previously reported in AMD-patients. Moreover, a slightly higher systemic exposure in subjects with DME cannot be excluded. Consequently, there may be an increased risk in subjects with DME, especially in cardiovascular high risk patients. The risk in these patients will be further addressed in the post-marketing study where subjects at risk (including previous cardio/cerebrovascular events, hypertension etc) will be enrolled.

In case of pregnancy during treatment with Lucentis, the information derived from the embryo-foetal study in monkeys gives assurance since no foetal adverse effects were observed. However, the exposure margin in this study compared to a worst case clinical exposure is limited (0.9-7-fold). Since VEGF inhibition has a potential to adversely affect the embryo-foetal development, there is a potential risk for adverse effects during pregnancy.

Benefit/Risk Balance

- Importance of favourable and unfavourable effects

Treatment with ranibizumab resulted in a clinically convincing and a statistically significant mean improvement of VA in subjects with DME. After 12 months treatment, the difference vs. sham treatment was 11 letters vs. sham injection and 6 letters vs. laser photocoagulation, in the RESOLVE and RESTORE studies, respectively. An important proportion, 40-62% and 23-36 % gained ≥ 10 and ≥15 letters in VA in the two studies. An increase of 15 letters may translate into benefits such as driving and reading.

Treatment is not without risks; however the risks, based on the submitted data, appear comparable to that previously identified in the AMD-population. Besides risks for the manageable increase in IOP and injection-related damage to intraocular tissues, rare, but important and potentially sight threatening risks are those associated with retinal detachment and endophthalmitis. The most important potential, although not frequent, non-ocular risks in DME patients seem to be those that are previously identified in patients with AMD, i.e. risks that may be related to systemic VEGF-inhibition.

- Benefit-risk balance

The natural progression of DME leads to vision loss of more than ≥ 10 letters of VA within 2 years in approximately 50% of patients. The only treatment and current standard of care is laser photocoagulation as it has been demonstrated to reduce the risk for severe decrease of VA (≥15 letters) with 50 % over 2-3 years. However, there is a substantial group of patients who are unresponsive to laser treatment and for whom no significant improvement in VA is to be expected. In comparison with laser photocoagulation, the risk profile in ranibizumab-treated patients is very different, and the immediate risk is estimated to be higher due to the IVT injection. However, laser photocoagulation is a destructive treatment and there is an important risk of damaging the centre of the macula, creating scotomas, when the leaks to be treated are close to the macula. Moreover, in the long term, repeated photocoagulation may impair peripheral vision since large parts of the retina will eventually be destroyed.

Despite the safety database being limited, Ranibizumab-treatment is the first treatment that has shown to increase VA in subjects with DME. From the submitted data, the magnitude of effect is considered to outweigh the risks, at least in the majority of subsets of the target population, since the strength of the efficacy data is convincing.

- Discussion on the benefit-risk balance

The current data show a benefit of ranibizumab as monotherapy that is considered to outweigh the identified as well as the potential risks.

The subjects in the safety database are sufficient to ensure that there is a 95% probability that a common AE in this population has been detected which is not the case for subjects that are also treated with laser. Thus, the safety database is still rather limited and less than common AEs are not characterised in this population. Although the non-ocular risk profile in diabetic subjects treated with ranibizumab appears reassuring, it cannot be excluded that the diabetes co-morbidity profile may put the target population at a higher risk. In addition, compared to the elderly AMD-population, diabetic patients are considerably younger and may be treated for several years. Even though long-term laser photocoagulations results in retinal scars that may impair vision, the potential complications after repeated long-term intravitreal injections are still not known.

The current standard of care in DME is treatment with laser photocoagulation to reduce the risk for a future, severe loss of vision. In clinical practice, subjects with DME may not have a visual impairment, but are nevertheless treated with laser photocoagulation. Treatment with ranibizumab will therefore introduce a new treatment paradigm, since only subjects with an impaired vision due to DME should be treated. Consequently, the treatment approach would be to treat the oedemas with laser photocoagulation and, when vision becomes impaired, start ranibizumab-treatment. This approach is in agreement with the new DME indication, the proposed re-treatment criteria and supported by the submitted data.

With only limited support for efficacy beyond 12 months, (in the form of 2-year data from a publication), it is not known whether there is a long-term benefit of ranibizumab-treatment (as established with laser) in subjects with oedema only. Therefore, the information to treat only the visual impairment has to reach the physicians. This will be done through using the educational material as specified in section 2.3. Although a large proportion of the retinal specialists are familiar with ranibizumab treatment in AMD, it is possible that a new subset of specialist will be introduced to treatment. As there are major risks if the injection procedure is handled incorrectly, there will be a need for a continuous education of physicians in this field and the educational programme for the AMD-population has been further adapted.

There is also only limited support for the safety of Lucentis beyond 12 months (again in the form of 2-year data from a publication). Although reassuring, the long-term data in this condition is too limited. Together with this arises the concern related to uncertainty if the 12-months gain in VA due to ranibizumab-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. Consequently, there is a need for long-term data. Such data will be available in 2012. On the other hand, since there were no additional treatment benefits with the combination of ranibizumab and laser, taking the destructive effects as well as the previously characterised benefits of laser into account, it remains unknown whether there is population that may have a benefit of the combination treatment. However, this will be further explored in a planned additional study.

Despite some limitations of the safety database, in view of the supportive data from ongoing and published studies together with the experience from the AMD-population as well as the planned 5-year post marketing observational efficacy and safety study, the above-mentioned uncertainties, including those related to the lack of safety data after long-term treatment, are considered possible to handle with post-authorisation commitments, additional updates of the SPC and the RMP.

Risk management plan

An update to the risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The CHMP endorsed that ongoing routine and additional risk minimisation measures in place for the AMD indication are extended to include the DME-indication.

Recommendation

Based on the CHMP review of data on safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Lucentis in the treatment of visual impairment due to diabetic macular oedema (DME) was favourable and therefore recommended the granting of a positive opinion to the type II application to extend the indication for DME.

Endocrinology, Metabolism and Cardiovascular

Arixtra (fondaparinux sodium) to include treatment of acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep vein thrombosis.

Benefit-Risk Assessment

The scientific interest in different treatment alternatives of SVT has been relatively limited so far. There are few or no large well designed trials investigating the benefit and risks of anticoagulant therapy in these patients. This may in part be due to the historically common view that SVT is a rather benign disease that could primarily be treated conservatively with e.g. elastic stockings and local treatment. An exception has been SVT in the V saphena magna extending close to the sapheno-femoral junction where surgery often has been regarded as indicated. However, in recent years the evidence has increased that SVT may be associated with a higher incidence of thrombotic complications from the deep venous system than previously anticipated. Furthermore, anticoagulant treatment has probably been rather extensively used off-label in clinical practice in patients with more extensive SVT, which also is reflected in some of the current guidelines. Thus, in this perspective, the relatively large, placebo-controlled study evaluating anticoagulant therapy supporting this indication is of considerable scientific interest.

Efficacy: The single pivotal study supporting the application was generally of an adequate design and seems to have been well performed. It provides convincing results with regard to the composite primary end point. The majority of primary end point events consisted of extension or recurrence of SVT. Such a reduction of extension and recurrence of SVT is, however, to be regarded as clinically meaningful and most probably results in reduced pain and symptoms related to the inflammatory process which sometimes can result in temporary walking disability. The reported significantly lower incidence of surgical interventions in the fondaparinux group provides additional support for the clinical relevance of the reported reduction in the incidence of extension or recurrence of the SVT.

The number of events with probably larger risks of severe complications (DVT or LE) was considerably lower. By treating 1500 patients 6 symptomatic cases of PE and 15 of DVT was prevented according to the results (p=0.015 and 0.001, respectively). However, such a reduction of risk has been accepted for wide spread prophylaxis in surgical patients at moderate risk.

The results were consistent over different demographic subgroups as well as in subgroups with different SVT characteristics and risk factors. It has been demonstrated by the MAH that treatment effects were similar in subgroups with different length of the SVT.

The recommended treatment duration has been discussed in relation to the CHMP questions and a duration of a minimum of 4 weeks with maximum 6 weeks is reflected in the revised SPC.

Safety: The reported bleeding rates were low. The bleeding risk in patients with SVT is not expected to be much different from the general population of the same age and gender distribution. However, treatment with NSAID or aspirin is probably not uncommon in these patients and thus they are expected to be at a somewhat increased risk for bleeding when treated with anticoagulants.

However, no apparent differences in bleeding rates between the treatment groups were reported overall or in the subgroups of special interest as those mentioned above. This probably reflects that the target population generally has a lower bleeding risk, as compared for example with surgical patients who are treated prophylactically with similar doses. Further characterisation of the bleedings has been provided in the responses to CHMP questions and these analyses are judged not to change the overall conclusions summarised above. In order to achieve similar exposure in patients with renal impairment (estimated CrCl 20-50 ml/min) as in the overall population and to reduce the risk for bleedings in these patients a reduced dose is recommended (1.5 mg). This is consistent with the dosing recommendation for prophylaxis in surgery patients.

As pointed out above it may have been difficult to capture subclinical bleedings with the chosen study design. No laboratory tests were done after screening and e.g. occult gastrointestinal bleedings could easily have been missed.

Conclusions on benefit risk balance

The benefit risk balance of the new indication is judged to be favourable.

Byetta (exenatide), to include treatment of type 2 diabetes mellitus in combination with thiazolidinedione (with or without metformin).

Benefit-Risk Assessment

In support of the extension of indication 4 clinical studies were submitted. One (GWAP) out of these 4 studies has already been assessed in the initial MAA. At that time point, this trial was deemed sufficient to assess efficacy, but the study duration was considered insufficient by the CHMP to determine the safety of exenatide with TZD. A new study has now been completed (Study GWCG, 26

weeks duration), and data is also available from two other studies (GWBG and GWAY) in which some patients are exposed to exenatide and TZD.

The study design and study populations are basically considered as acceptable. However, the number of patients on monotherapy with TZD at the time of inclusion was limited (n=33) and these patients may not have been representative for the restricted EU monotherapy indication for TZDs. However, according to further analyses by the MAH, 21 of these patients may have been representative according to European standards.

Benefits

Concerning efficacy associated with the addition of exenatide to TZD + metformin, exenatide was superior to placebo and the treatment resulted in clinically relevant reductions of HbA1c in the pivotal studies GWAP and GWCG (mean reductions - 0.74 and -0.84 %, respectively). Furthermore, in study GWBG, exenatide was non-inferior to insulin glargine concerning reduction of HbA1c and in study GWAY, the addition of exenatide +rosiglitazone resulted in a more pronounced reduction of HbA1c compared to either of the drugs alone. Thus, a clinically relevant effect of the addition of exenatide to TZD + metformin is indicated by these results.

Risks

As mentioned above, the main reason why the combination of exenatide with a TZD was not approved at the time of MAA, was the limited data concerning safety (121 patients treated for 16 weeks). The exposure is now increased to 346 patients out of whom 125 had exposures 6 to 18 weeks, 180 had exposures 18 to 32 weeks, and 17 had exposures ≥32 weeks. Approximately 90 % of these patients were treated with exenatide+TZD+ one or more additional drugs (most often metformin). Concerning safety in these patients, as expected, GI adverse events were common in exenatide treated patients. However, the combination with TZD did not seem to increase the incidence of GI symptoms compared to other exenatide combinations. Neither were there any signs of an increased risk of oedema when exenatide was added to TZD compared to placebo. No serious cardiac disorders, cases of treatment related renal failure or cases of pancreatitis were reported, but it should be remembered that only 17 patients had an exposure longer than 32 weeks. No new adverse event reactions, beyond those already provided in the SmPC for the current metformin plus sulfonylurea indication, were identified by examination of the TZD data by itself.

The target population for dual therapy with TZD + exenatide (patients inadequately controlled by diet and exercise for which metformin is inappropriate because of contraindications or intolerance) is not the same as for triple therapy. Patients treated with TZD monotherapy due to intolerance to Met is not likely to differ from the population treated with dual therapy, Met+TZD, and for these patients efficacy and safety data could be extrapolated between populations. The patients with contraindications to Met may on the other hand be a more vulnerable population including patients with renal/hepatic impairment and cardiac disease. However, considering the warnings and contraindications for TZD, only patients with renal impairment would be eligible for TZD monotherapy. Considering that exenatide is not recommended in patients with severe renal impairment, it is indeed agreed that the target population in Europe for the TZD+exenatide combination is likely to be small. Still, some reassurance concerning efficacy and safety is needed and it is questioned whether data from 21 representative patients is sufficient. Considering the target population (patients with mild/moderate renal impairment), the adverse events potentially expected could be oedema (fluid retention) and more pronounced gastrointestinal side effects (patients with moderate renal impairment have a 36% lower clearance of exenatide). Based on the results in study GWAP as well as on the analyses of TZD only users in all studies (presented in the MAHs response), these potential issues were not confirmed. The

safety profile in the dual therapy group was similar to the triple therapy group. Concerning alternative add-on treatments for patients on TZD monotherapy, SU as an alternative treatment to exenatide can lead to hypoglycaemia and weight increase, although the long term experience of SU speaks in its favour. Insulin, on the other hand, should in general be avoided in combination with TZD due to the risk of fluid retention.

Balance

Submitted studies show that exenatide added to TZD with or without metformin, results in a clinically relevant glucose lowering effect without any new, unexpected safety concerns compared to previously approved combination indications. The benefit/risk balance is therefore considered as positive and the variation is approvable. Considering the small target population for the TZD+exenatide combination, the very limited safety data presented was considered as acceptable. The dual therapy indication is therefore considered as approvable.

Cholestagel (colesevelam) to extend the therapeutic indication, to include combination treatment of colesevelam with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.

Benefit-risk assessment

- Discussion and conclusions on Environmental Risk Assessment

The applicant has not submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline. The CHMP is of the opinion that the applicant has not sufficiently demonstrated that no increase in use will occur due to the extended indications applied for and thus, further investigations should be performed. The applicant has provided a commitment to submit the documentation within a specified timeline.

- Discussion and conclusions on efficacy

The applicant provided two studies to show that colesevelam has additional benefit in reducing LDL-C when added to ezetimibe with/without statin as a third line lipid lowering strategy.

In study CHOL00107, a 12% reduction in LDL-C levels was achieved when colesevelam was added to a maximal tolerated therapy with a statin and ezetimibe. The observed lipid lowering effect was slightly less to that in monotherapy (-15% to -18%) and similar to the effect when colesevelam is added to statin alone (-8% to -16%) or fenofibrate (-10%). However, the absolute reduction of 0.5 mmol/l can be considered a relatively modest effect. . The reduction resulted in only 9% of patients reaching the treatment goal (<2.5mmol/L LDL-C) or 30% were considered as responders (<15% decrease in LDL-C). Nevertheless, this patient population could be considered as therapy resistant patients, who despite being on already high dose combined lipid lowering therapy still do not reach treatment goals. Therefore, the sought third line therapy option of colesevelam could be considered a welcome addition to existing treatment possibilities and is considered acceptable. An additive lipid lowering effect is observed that fits with the complementary pharmacological mechanism of action of colesevelam.

Study WEL408 has been submitted previously. Results of this study have also been assessed, but could not be included as benefit was actually only demonstrated in the setting of ezetimibe and colesevelam duotherapy; for which there was only a very small target population Therefore, it was decided in line with the SmPC guideline not to include this information in section 5.1 of the SmPC as this should be limited to data covered by the that time approved indication; either combination therapy with statin or colesevelam as monotherapy. Study WEL408 demonstrated that an additive LDL-C lowering effect is observed when colesevelam is combined with ezetimibe. Triglycerides are negatively but statistically

non-significantly affected by colesevelam co-medication. However, when simvastatin was added to the combination the LDL-C in a second treatment period, declining efficacy of colesevelam disappeared in the triple therapy.

The apparently discrepant finding in the added efficacy of colesevelam in triple therapy is largely explained by the differences in study design. Study WEL408 was not properly designed to demonstrate additional effect of colesevelam when statin is added afterwards. Study WEL408 supports the principal place of statins in treating hypercholesterolaemia, as much more effective reductions in LDL-C can be achieved even when statin is added on top of already combined lipid lowering therapy. Study WEL408 can be considered supportive as it confirms the finding of CHOL00107 that colesevelam when added to an ezetimibe containing lipid lowering therapy is still able to reduce LDL-C further. It is acknowledged that power issues may have contributed as well in not finding a differential impact of a colesevelam-based strategy in the second phase of study WEL408. Nevertheless, following the evaluation of the results of study CHOL00107, an indication for dual colesevelam and ezetimibe therapy and inclusion of information in section 5.1 could be supported for patients who cannot tolerate, or for whom statins are contra-indicated and are inadequately controlled by ezetimibe monotherapy. The posology for the colesevelam maintenance dose for concomitant use with statins and/or ezetimibe remains to be 4 to 6 tablets.

The concomitant dosing of ezetimibe with colesevelam was justified and is supported. It was demonstrated that in four retrospective small studies separate or concomitant dose intake did not influence outcome results. In addition, based on pharmacokinetics it was justified that it would not be very useful to separate dosing schedules because of the enterohepatic cycling of ezetemibe. The proposal to change the posology and exclude the separated intake of these medicines is therefore considered acceptable.

- Discussion and conclusions on safety

Conclusions on safety based on these two studies are limited, as limited numbers of patients have been studied. With the introduction of colesevelam to the therapy, both studies demonstrated a higher incidence of adverse events. However, the adverse events profile was mild to moderate in severity. Still, adding colesevelam to existing lipid lowering therapy increases the occurrence of gastro-intestinal adverse events, as was expected. In addition, the applicant should discuss in the next PSUR cycle whether some adverse events identified in the pooled safety data set warrant inclusion in the safety section of the SmPC.

- Overall conclusions

In conclusion, colesevelam demonstrated moderate LDL-C lowering capacity in duo therapy and triple therapy with statins and statins + ezetimibe, respectively. This could lead to a third line indication in patients on a maximal tolerated therapy with a statin and ezetimibe. Also, the indication can be extended to patients who cannot tolerate or for whom statins are contra-indicated and are inadequately controlled by ezetimibe monotherapy. Particularly gastro-instestinal adverse events were noticed, but these are known adverse events for colesevelam as well as of ezetimibe. Still, as these adverse events are only mild to moderate of origin, the benefit risk profile can be considered positive as third line therapy for patients in whom treatment goals cannot be achieved with statins and ezetimibe or ezetimibe alone when statin therapy is not feasible.

- Paediatric data

Study WEL410 has been previously assessed in FUM 007.2. No changes to the SmPC based on these results where proposed at the time, but the MAH was asked to include these with the current variation procedure.

The CHMP is of the opinion that study WEL410, which is contained in the agreed Paediatric Investigation Plan and has been completed after 26 January 2007, is considered as significant.

The main goal of study WEL410 was the demonstration of efficacy in paediatric patients of colesevelam added to the statin or as monotherapy. Considering that the current guidelines recommend statins as the first line therapy in paediatric HeFH, it would have been expected to recruit patients intolerant or contraindicated for statins, in the monotherapy indication. This was not the case. However, this was already implemented in the adult clinical studies, in which statin-naïve patients were recruited for the monotherapy studies, who were not necessarily intolerant to statins. Therefore, it can be generally concluded that the monotherapy indication falls within the adult indication. The results show that colesevelam significantly reduced LDL-C in a consistent and dose dependent manner to -11.9% using the higher dose of 3750 mg. This is somewhat less than reported in adults (-15% reduction in LDL-C) and much less than reported for statins in the paediatric population (-22.9% reduction in LDL-C for pravastatin). Cholestagel can still constitute a therapeutic option for paediatric patients with statins intolerance; however, experience is limited to 28 weeks. Long term safety data are lacking.

Regarding the add-on therapy, the efficacy was investigated only in 48 patients, which is considered to be a rather limited population. Patients were not on the maximally tolerated dose of statin, precluding a conclusion on the actual additive effect of colesevelam on optimal statin therapy. A trend for reduction of LDL-C is shown in patients on the higher dose colesevelam, and a trend for increase in LDL-C was seen with the lower dose of colesevelam and placebo groups. The increase in LDL-C could be attributed to patients stopping their co-administered statins, but this possibility is not further verified. No firm conclusions can be made regarding the efficacy of colesevelam as an add-on therapy due to the study shortcomings, in particular the small number of patients. Whether patients need to be on the highest dose of statin before administering clovesalam is a point for discussion. Compliance issues with respect to statin use may be better addressed by evaluating LDL-C effects corrected for placebo.

Short term safety seems to be in line with the safety profile already known from the adult population. Gastro-intestinal problems and adverse events related to myopathy were observed, but no new safety signals were identified. Long term data are lacking.

In conclusion, the benefit risk ratio for treatment of paediatric HeFH patients on top of statins is considered inconclusive. The number of patients on statin therapy was very small and no efficacy was shown for colesevelam. The benefit risk ratio for monotherapy with colesevelam is more positive, but long term safety data are lacking.

Relevant information on the use of colesevelam in paediatric population was included in sections 4.2 and 5.1 of the SmPC.

Furthermore, the MAH proposed to update section 4.5 of the SmPC with the information on the effect of Cholestagel on the bioavailability of lovastatin, which was agreed with the CHMP.

- Risk Management Plan

The MAH submitted a risk management plan. The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information. Annex II have been updated with standard wording to reflect the RMP version agreed with the CHMP.

Oncology, Haematology and Diagnostics

Mabthera (rituximab), to include the treatment of follicular lymphoma patients responding to induction therapy.

Benefit-risk assessment

Benefits

- Beneficial effects

The data presented from the pivotal PRIMA trial and the supporting ECOG 1496 trial showed that rituximab maintenance therapy every two months for two years gives a significant improvement of PFS in patients with advanced follicular lymphoma who have responded to standard induction chemotherapies. PFS has been recognized by the CHMP as a relevant primary endpoint in this clinical situation, and as such, an improvement in PFS may be of clinical relevance.

The results of the PRIMA study showed that the 25th percentile PFS for patients on observation was 16.7 months and for patient on rituximab maintenance was 36 months, with a HR 0.50 [(CI 0.39; 0.64), investigator based] or 0.54 (IRC-based). However, it is difficult to evaluate the absolute PFS gain with nearly 75% of the patients still classified as responders at the end of the maintenance phase. The median has not been reached in the investigator-assessed dataset. For the IRC-assessed dataset the median PFS gain is 6.2 months (from 30.9 to 37.1 months). In the context of a very long natural history (median OS about 10 years) of the targeted disease, the long-term benefit of this gain is still uncertain.

Furthermore, there is no difference in OS for the two treatment strategies (observation vs. maintenance).

On the positive side, rituximab maintenance significantly delays time to next anti-lymphoma therapy by a year (a secondary endpoint) and may decrease the transformation rate (non statistically significant result). More patients are classified as responders (CR/CRu/PR) at the end of maintenance therapy (74% versus 55%).

The results of the supportive ECOG1496 were comparable to the results of the PRIMA study: a statistically significant increase of the PFS was observed (HR of 0.37 with a CI of 0.25; 0.56) after rituximab maintenance therapy in comparison with observation only. The PFS improvement in this study seems to be even better than in the PRIMA study. However the benefit might be overestimated as the patients included in the observational arm didn't receive rituximab at any moment of the trial.

- Uncertainty in the knowledge about the beneficial effects

A median follow-up of about 2 years is relatively short for the assessment of long-term benefit of rituximab maintenance although the cut-off date allows a final analysis of the primary endpoint PFS. Taking into account that all patients will have a continuous pattern of relapse and retreatments, it is not realistic to evaluate the influence of rituximab maintenance on OS. However, patients must be followed up for PFS and OS for at least five years, final OS data should be submitted in time (FUM).

There certainly are data to support that a long remission after first-line therapy predicts a better response to subsequent therapies and a longer survival. However, as maintenance therapy after first-line treatment has yet to show an OS benefit, the biology may be different in patients who relapse on the background of rituximab maintenance therapy than in patients who have only been observed. The rituximab resistance rate after rituximab maintenance therapy at first remission has not been studied.

More data about the rituximab resistance rate as the result of post-first line maintenance therapy are needed to estimate this effect on the success (response, PFS, OS) of eventual rituximab retreatment.

Both the pivotal study and the supportive study showed a clear trend towards a lower HR for PFS events in younger patients (0.45 in patients < 60 yrs. vs. 0.59 in patients > 60 yrs in the PRIMA trial). One might suspect that the benefit is further diluted in even older patients, e.g. patients > 70 year, who make up a considerable fraction of follicular lymphoma patients (25-30 %), according to a Dutch population-based registry study (Maartense et al. (2002), Ann Oncol 13(8): 1275-1284.) and approximately 20% in the ECOG 1496 study. Further subgroup analyses of the PRIMA trial (for which the trial is not powered) indicate that patients older than 70 or 75 years may have lesser benefit from rituximab maintenance therapy (HRs between 0.80 and 1.15, with very wide confidence intervals). A further subgroup analysis of the elderly patients is needed when more mature data become available, with more events making the subgroup statistics more meaningful.

The PRIMA study included only patients with a high-tumour burden according to the GELF criteria and it is not entirely clear whether the data can be extrapolated to all patients with follicular lymphoma.

However, the supportive ECOG study included patients with stage III-IV according to the Ann Arbor staging system making the claimed indication reasonable.

Risks

- Unfavourable effects

Safety data from the pivotal PRIMA trial are in line with the SmPC and previous post-marketing experience for this monoclonal antibody that has been marketed in the EU since 1998. The important difference in safety is a clear increase in the incidence of infections and leuko-/neutropenia in patients treated with rituximab as maintenance. There is an increased incidence of SAEs related to infections, cardiac disorders and gastrointestinal disorders in the rituximab arm. The numbers are still rather low (maybe even if compared to an age-matched background population).

There is a clearly increased incidence of infectious AEs and SAEs in the rituximab arm. While the difference is clear regarding SAEs, the numbers are quite low (25 infectious SAEs in the rituximab arm and 6 SAEs in the observation arm).

The data do not raise concerns about a high risk of HBV reactivation during rituximab maintenance therapy. As in other studies, it is uncertain whether the observed sporadic occurrence of PML is secondary to rituximab or to previous chemotherapy/compromised immune system function. Unconfounded cases of PML have been reported in patients with RA treated with rituximab.

Furthermore, significant laboratory value differences between the rituximab and the observation arms are the suppressed level of B-cells and the (usually within normal ranges) reduced immunoglobulin counts in the rituximab arm.

It is reassuring that the numbers of deaths are lower in the rituximab maintenance arm with regards to both lymphoma-related and non-lymphoma-related deaths.

- Uncertainty in the knowledge about the unfavourable effects

Relatively few elderly patients (>75 yrs) were included in the pivotal study. AEs and SAEs do not seem to increase with age. However, the elderly patients selected for a randomised trial do not necessarily reflect an age-matched background population for which we are concerned when considering the risk/benefit balance.

Balance

- Importance of favourable and unfavourable effects

It is a dogma in cancer therapy that achievement of durable remission is of clinical benefit because eradication of all neoplastic cells is a prerequisite for long-term cure. A lesser reduction in the tumour burden for a period of time may also be of clinical benefit. Therefore, PFS represents an accepted intermediate efficacy endpoint. PFS should generally be supported by a prolongation in OS. However, considering the very long natural history for patients with newly diagnosed follicular lymphoma with a median survival of about 10 years, PFS remains the only realistic efficacy endpoint. In evaluating the importance of a clear PFS gain as shown in this application, one has to take into account the natural course of disease of patients with follicular lymphoma. The disease usually follows an indolent course with a continuous pattern of relapses after each therapy, the remissions having decreasing duration with increasing number of retreatments. In younger and middle-aged patients the cause of death is most commonly the lymphoma or the therapy related with secondary malignancies. At the time of death many patients will have had transformation to a more malignant aggressive lymphoma.

On that clinical background a PFS gain in a rather narrow time window cannot stand alone as measure of clinical benefit. Significant PFS gain has been adequately demonstrated by the pivotal and supportive study. The primary endpoint is supported by a higher response rate at the end of maintenance therapy (75%) compared to a rate of 55% in patients also reflected in a delay of 12 months in time to next therapy. Since such therapy most probably will comprise cytostatics, this delay is considered to be of clinical benefit. There are also data to support that a long remission after first-line therapy predicts a better response to subsequent therapies and a longer survival. However, these data are mainly derived from clinical series without maintenance and it is uncertain whether the findings can be extrapolated to the population in question. A high response rate will most probably also mean less constitutional symptoms but this effect has not been specifically addressed in this application. Finally, there are no indications that rituximab maintenance enhances the risk of histological transformation. Although insignificant so far, the incidence of transformation may be lower in patients receiving maintenance therapy.

On the negative side, the burden of additional maintenance therapy in terms of toxicity should be taken in account. The known safety profile of rituximab remains unchanged when the antibody is used as maintenance every two months for two years. The mortality is numerically lower in the maintenance group both in relation to lymphoma deaths and non lymphoma deaths.

Therefore, no serious unfavourable effects have been detected.

Benefit-risk balance

- Discussion on the benefit-risk assessment

The application has demonstrated a very clear gain in PFS supported by a higher remission rate at the end of maintenance, a delay in the time to next antilymphoma therapy and a potential lower rate of histological transformation.

No serious safety concerns have been identified.

Therefore, the CHMP considered that the Benefit-Risk ratio of rituximab for the treatment of follicular lymphoma patients responding to induction therapy is positive.

All the proposed consequential changes to sections 4.1, 4.2, 4.3, 4.4, 4.8, 4.9 and 5.1 of the SmPC and to the Package Leaflet were agreed.

Further, the MAH has updated annex IIB to reflect the latest version of the Risk Management Plan (version 5.1) agreed with the CHMP, which is acceptable. Minor editorial changes have also been implemented.

Mabthera (rituximab), update of section 4.1 of the SmPC with information of improvement in physical function and reduction in the rate of joint damage as measured by x-ray, when given in combination with methotrexate.

Benefit-risk assessment

The proposed indication for rituximab in combination with chemotherapy in patients with relapsed/refractory CLL is based on data from one pivotal study (BO17072 -REACH). This was a multicentre/multinational, open label, prospectively planned, randomised controlled study. In this study 552 patients were randomly assigned to treatment groups through a central randomisation to either the combination of R-FC or FC alone. In view of current practices in this patient group the choice of the treatment modalities and schedules in the active and the control arms are considered justified.

Although a pre-planned interim efficacy analysis of study BO17072 was performed after two-thirds (190/284 planned, 205 actual) of the events (progression or deaths) had been reported, it was decided that PFS did not cross the pre-specified threshold at that time (actual result: p=0.012) and, because all patients had completed therapy, the data monitoring board recommended that the study should be continued until the final analysis. As a consequence, only results from the final analysis (data cut-off July 23 2008) were submitted.

The primary endpoint was the Progression-free Survival (PFS); the secondary endpoints included the Event-free Survival, Overall Survival (OS), Disease-free Survival (DFS), Overall Response Rate and Time to new CLL Treatment. Although in general PFS is considered a surrogate endpoint when assessing efficacy, in the setting of 2nd line treatment of CLL this endpoint can nevertheless be considered of clinical relevance especially when assessment of OS may be hampered by the effect of next line therapies.

The patient population studied can be considered as representative for the general population with relapse or refractory CLL and baseline characteristics appeared balanced between the two treatment arms. Patients with ECOG PS >1 were not eligible.

Results from BO17072 on PFS showed substantial improvement of PFS: The KM estimate in the ITT population showed median PFS of 20.6 months with FC versus 30.6 months with R-FC. This difference is statistically significant (p=0.0002) and the HR was 0.65 (95% CI 0.51 - 0.82). Therefore this pivotal trial BO17072 data on PFS showed a statistically significant and clinically relevant improvement of the Progression free Survival. In addition, an increase in Event-free Survival and overall Response Rate confirmed the benefit for rituximab plus FC in patients with relapsed or refractory CLL. Although a trend towards an OS benefit is envisaged, formal proof of benefit in survival is lacking possibly due to next line treatments and also QoL improvement was not demonstrated.

The treatment benefits observed with R-FC were seen in nearly all of the subgroups analyzed except for patients that relapsed >10 years after initial treatment and for patients with CD38 negative CLL phenotype (a prognostic favourable subgroup). From the supportive studies it may be concluded that the addition of rituximab to various appropriate other chemotherapy regimens for relapsed CLL improves efficacy regarding PFS, although also here, as in trial BO17072, indications of survival benefit are limited.

With regard to safety, the risks of rituximab in CLL patients were comparable to known safety profiles of rituximab used in approved indications in combination with other cytotoxic chemotherapy regimens.

In particular, higher incidences of neutropenia, leukopenia, febrile neutropenia and pancytopenia were also seen in patients treated with rituximab for 1st line treatment of CLL and in NHL. The addition of rituximab did not increase the rate of treatment discontinuations due to toxicity or the incidence of treatment related deaths compared to FC alone.

Myelotoxicity, hepatitis B and secondary neoplasms were more apparent in the R-FC arm. Overall, the benefits of the addition of rituximab to the combination fludarabine and cyclophosphamide with regard to PFS outweigh the risk related to this addition. The PFS benefit in relapsed or refractory CLL is substantial, 10 months, and this clearly reflects a clinically relevant advantage. Although OS benefit could not be proven, it can be envisaged that rituximab leads to prolonged survival as well. Therefore the benefit/risk ratio is considered positive.

The application could be approvable, provided other concerns are resolved. The indication for first line treatment of chronic lymphocytic leukemia (CLL) was recently approved. Consequently, it can be foreseen that in future patients, that may encounter refractoriness to 1st line treatment, or patients that may relapse after initial treatment, will have had rituximab as part of prior first line therapy.

Study BO17072 excluded patients who were previously treated with rituximab or other monoclonal antibodies. At the time of study planning in 2001 and 2002, patients who had received monoclonal antibody treatment in the first-line setting were considered rare as no monoclonal antibodies were approved for the first-line treatment of patients with CLL. Standard first-line treatments were mainly fludarabine monotherapy and chlorambucil (with or without corticosteroids), the two first-line regimens that contributed most to the patient pool in study BO17072 (REACH).

During the last 5-7 years, use of first-line fludarabine and cyclophosphamide (FC) combinations has increased as a result of a number of randomised phase III trials showing superiority of fludarabine over chlorambucil, and of FC over fludarabine monotherapy. Meanwhile, the ML17102 (CLL-8) trial has demonstrated that the addition of rituximab to FC (R-FC) is superior to FC alone, with higher response rates and complete response (CR) rates, and longer progression-free survival (PFS) reported. Accordingly, it is expected that R-FC will rapidly become the combination of choice for patients with previously untreated CLL who are suitable for fludarabine-based therapy. However, the ML17102 (CLL-8) study data also indicate that although patients treated with R-FC benefit from the prolongation of PFS, ultimately most patients will still relapse and require further therapy. Limited data that are available from approximately 180 patients demonstrate that rituximab-containing regimens, specifically repeat administration of R-FC (and variants thereof) are a viable and useful therapeutic option for patients whose initial treatment contained rituximab. There is no data published indicating that regimens that do not contain rituximab produce better outcomes than regimens that do incorporate rituximab. An exclusion of CLL patients who have previously received rituximabcontaining therapy from treatment with rituximab-containing combinations at relapse would limit the available options therefore it was considered appropriate to leave the treatment decision to the clinician.

The overall results of salvage therapy after first-line FCR therapy are unsatisfactory as stated by Keating et al. That fact may be due both to refractoriness to the two most important classes of cytotoxics for CLL, *alkylating agents* (cyclophosphamide) and *fluoropyrimidines* (fludarabine), and to *anti-CD20* therapy (rituximab). It seems much more likely that refractoriness to conventional chemotherapy plays a major role in the unsatisfactory second-line response than the limited contribution of rituximab. Therefore, a restrictive wording as regards rituximab is not justified. However, it seems that the results from study BO17072 may not be fully translated to that particular population of CLL patients. If FCR becomes standard first line therapy for CLL patients who can tolerate this regimen the same regimen may not be generally appropriate as second-line therapy. The decision to use FCR as second-line therapy in that population may depend on a number of other factors (primary refractoriness to FCR, early relapse after initial FCR, long disease-free interval after FCR,

patient tolerability and performance status etc.). Such clinical decisions are not easily transferable to the SPC wording, hence the following statement was agreed: "Limited data on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to fludarabine or any nucleoside analogue are available."

Rituximab is currently not licensed in paediatric NHL. The MAH is working with paediatric collaborative groups to support a randomised international clinical trial in which about 300 paediatric patients will be treated with rituximab (plus 300 controls), and in which all adverse events will be collected up to 5 years. In addition, the MAH is planning to implement an enhanced pharmacovigilance system in August 2009, which will proactively follow up all paediatric adverse event reports received by the MAH, including reports of 'off-label' use. This will utilise a 'guided questionnaire' to better characterise the reports. The guided questionnaires will be 'tracked' and followed up closely. This information will be included in the periodic safety update report (PSUR) which is submitted to the EMEA on a regular basis. Both these proposals have been described in the rituximab Paediatric Investigation Plan.

The MAH confirmed that collection of overall survival data will continue. The MAH intends to submit one updated analysis on overall survival with a clinical data cut-off approximately 24 months after the cut-off for the final analysis (data cut-off for final analysis was July 23, 2008). The up-dated OS data will be submitted to the EMEA about 5 months later, ie around Dec 2010. It is expected that with this additional follow-up, about 40-50% of deaths will have been observed in the BO17072 (REACH) study. Further follow-up for survival is not planned after the 2010 cut-off, since results of the primary analysis of the study were released to the public in November 2008 and substantial cross over to rituximab is expected to occur which will confound any future analyses. Accordingly, it is considered unlikely that an OS benefit will be observed at the next OS update or subsequently.

Benefits

Superior efficacy for the primary endpoint PFS has been convincingly demonstrated in favour of the rituximab containing combination. The primary endpoint of PFS was prolonged by a median of 10 months (20.6 months for FC and 30.6 months for R-FC) and the risk of disease progression or death was reduced by 35% when rituximab was added to the FC regimen (p=0.0002, Log-Rank test). This PFS benefit was robust and apparent in almost all of 48 pre-specified subgroups.

In addition, an increase in Event-free Survival and Overall Response Rate confirmed the benefit for rituximab plus FC in patients with relapsed or refractory CLL. Also a trend towards an OS benefit is envisaged, but as the overall survival data may be hampered by subsequent treatment options, the data may be difficult to interpret.

From the supportive studies it may be concluded that the addition of rituximab to various appropriate other chemotherapy regimens for relapsed CLL improves efficacy regarding PFS, although also here indications of survival benefit are limited.

Risks

With regard to safety, the risks of rituximab in CLL patients were comparable to the well known safety profile of rituximab. The safety profile of rituximab plus FC was very acceptable with only the expected addition of rituximab-related side effects to those of FC (more infections and more infusion related events).

The patient numbers included in the analysis might have been too small to detect prognostic factors for secondary malignancies. Inclusion of "second malignancies" as a potential risk for NHL and CLL in the RMP is accepted. Routine pharmacovigilance activities including discussion and monitoring of second

malignancies from spontaneous reporting and other sources in PSURs is considered sufficient at this moment. For each case report of second malignancy the MAH should analyse and report whether a causal relationship between the event and rituximab can be excluded. The overall discussion of second malignancies should always be based on cumulative data from all sources (all reports up to the data lock point). The MAH commits to provide the relevant information as asked for in the next and following PSURs.

Balance

Overall, the benefits of the addition of rituximab to the combination fludarabine and cyclophosphamide with regard to PFS outweigh the risk related to this addition. The PFS benefit in relapsed or refractory CLL is substantial, 10 months, and this clearly reflects a clinically relevant advantage. Although OS benefit could not be proven, it can be envisaged that rituximab leads to prolonged survival as well. The benefit/risk ratio is considered positive, as the MAH revised the SPC according to the CHMP recommendations provided and committed to provide follow-up information.

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

Sprycel (dasatinib), an orphan medicine to include the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in the chronic phase.

Benefit-risk assessment

Benefits

- **Beneficial effects**

The efficacy of dasatinib in newly diagnosed patients with CML-CP has been evaluated in a Phase III, open label, randomised superiority trial (study CA180056 or DASISION) comparing dasatinib 100 mg QD with imatinib 400 mg QD. A total of 519 patients were randomised, 259 patients in the dasatinib group and 260 patients in the imatinib group.

The open-label design is considered acceptable as the majority of the endpoints are objectively determined i.e. cytogenetic, molecular and haematological endpoints.

The primary endpoint was cCCyR rate at 12 months. This endpoint is widely accepted as a surrogate of clinical benefit and the adequacy of the primary surrogate endpoint stems from an analysis of the IRIS trial showing that CCyR at 1 year is predictive for PFS. This surrogate endpoint should be supported by time-dependent endpoints such as PFS and OS. In that context it should be taken into account that the overall 7-year survival rate for patients with newly diagnosed CML-CP treated with imatinib is now estimated to be 86 %.

Treatment with dasatinib produced a significantly ($p < 0.007$) higher cCCyR rate within 12 months (77%) compared with imatinib (66%) meeting the primary endpoint. The primary endpoint is supported by the secondary endpoints MMR at any time, Time to cCyR at any time and Time to MMR.

The PFS rates at 12 months are 96.4% (dasatinib) and 96.7% (imatinib), and the OS rates at 12 nonths are 97.2% (dasatinib) and 98.8 (imatinib). The PFS and OS data are still immature but will be provided post authorisation. Also, the rates of progression to CML-AP or CML-BC cannot be reliably assessed at this point in time.

Overall, study CA180056 convincingly demonstrates a favourable effect of dasatinib in comparison with imatinib in the first line treatment of patients with CML in chronic phase.

- Uncertainty in the knowledge about the beneficial effects

Efficacy in terms of cCCyR beyond 12 months is not known. Time-dependent endpoints are needed for a more definitive assessment of long term efficacy. At present OS and PFS are still immature but no detrimental effect is seen in the dasatinib group or the imatinib group. The MAH committed to provide yearly updates of the results from the trial.

If dasatinib substitutes imatinib as the preferred first-line treatment for CML-CP there is no evidence-based second-line therapy for patients failing dasatinib. However, this important clinical issue is not expected be resolved by the applicant at this point in time. However, the MAH committed to make proposals to prospectively collect response data (type, magnitude and duration) in patients receiving second line therapy after relapse or disease progression with dasatinib.

Risks

- Unfavourable effects

The observed safety profile for imatinib and dasatinib in the pivotal study was consistent with the known safety profile for both compounds. There were no new or unexpected major findings. Dasatinib is overall well tolerated. The safety profile of dasatinib has some differences compared to the safety profile of imatinib, however, it is not worse and acceptable in the proposed indication.

Pleural effusions are known to be associated with dasatinib, oedema and muscle cramps with imatinib. These findings were confirmed in the pivotal study. Pleural effusion was the most common fluid retention in the dasatinib group (10% vs. 0%) but discontinuation overall due to pleural effusion is infrequent. All pleural effusions were grade 1 to 2. Most often the dasatinib treated subjects with pleural effusions were managed by interruption of dasatinib but diuretic, dose reduction, corticosteroids and one thoracocentesis were also used. Three subjects discontinued due to pleural effusion. Pleural effusion did not in general impair the ability of subjects to obtain a CCyR or achieve MMR.

With regards to haematological toxicity dasatinib differ from imatinib by higher rate of grade 3 to 4 thrombocytopenia (19.1% vs. 10.5%). Most subjects had some degree of cytopenia on study; however, the majority was grade 1 or 2.

Another safety issues to be mentioned is the rate of abnormally elevated pulmonary artery systolic pressure (> 40 mmHg) which was found in 5.8% in the dasatinib group vs. 2.7% in the imatinib group.

- Uncertainty in the knowledge about the unfavourable effects

When pleural effusions (or other conditions) are treated with interruption of dasatinib or dose reduction it is not known if the duration of efficacy is sustained or the subjects will progress earlier. This, although the subjects in general did not have their ability to obtain a CCyR impaired in the pivotal study.

Also, the etiological relevance of dasatinib treatment to cardiac dysfunction, including cardiac failure, conduction disturbances, ischemia and myocardial infarction doesn’t seem well defined or quantified.

The relation of haemorrhage to thrombocytopenia or to other haemostatic defect secondary to dasatinib is not fully clarified.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The higher cCCyR within 12 months achieved with dasatinib as compared to imatinib are very promising results indicating substantial higher efficacy for the second generation TKI dasatinib as compared with the hitherto standard of care of patients with newly diagnosed CMP-CP.

The observed safety profile for dasatinib in the pivotal study was consistent with the known safety profile. There are so far no indications that dasatinib has any detrimental effects on OS as compared to imatinib.

- Benefit-risk balance

In conclusion treatment of first line CML-CP subjects show clear superiority of efficacy in the dasatinib group compared to the imatinib group. Long term efficacy results are warranted, and should be submitted postapproval. The safety profile of dasatinib is in some aspects different from that of imatinib but not worse, and overall manageable.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Sprycel in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase was favourable and therefore recommended the granting of this extension of indication.

In addition, the CHMP, with reference to Article 8 of Regulation (EC) No 141/2000, considers Sprycel not to be similar (as defined in Article 3 of Commission Regulation (EC) No 847/2000) to Glivec and Tasigna for the same therapeutic indication.

Sutent (sunitinib), to include the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

Benefit-risk assessment

Benefits

The primary objective of the study was PFS. Sunitinib 37.5 mg on a CDD schedule resulted in a median PFS of 11.4 months vs. 5.5 months in the placebo arm (hazard ratio 0.418, p=0.0001, 81 PFS events), thus translating into more than a 2-fold reduction in the relative risk of disease progression or death in subjects with pNET.

PFS improvement was observed independently of baseline histology, Ki-67 index (exploratory analysis only), disease burden, amount of prior therapy, and time from diagnosis.

Improvements in the secondary efficacy endpoints of ORR (9.3% vs 0%, p=0.0066) and OS (HR 0.409, 95% CI 0.187, 0.894, p=0.0204, 30 OS events) in the sunitinib arm was also observed.

Additionally fewer subjects treated with sunitinib than placebo started the use of disease-specific concomitant medications such as somatostatin analogs while on study.

- **Uncertainty in the knowledge about the beneficial effects**

In general, all supportive analyses submitted by the MAH showed consistency of the results with the primary analysis. The robustness was further corroborated by the complimentary PFS analysis based

on derived tumour assessments and in the IRC-based PFS analysis. Data on efficacy of sunitinib in the treatment of pancreatic NET from both pivotal Study A6181111 and supportive Study RTKC-0511-015 are supporting of the substantial clinical benefit to patients with this relatively rare form of pancreatic cancer for whom approved or effective treatment options are currently unavailable.

Although the study was designed with an interim analysis at 130 PFS events and a final analysis at 260 events, the DMC recommended in February 2009 that the study be closed based on their review of safety and efficacy data after 73 events had been recorded.

A major issue has been the robustness of the efficacy results because the DMC was supplied with efficacy data during the 3 safety reviews when only 1 interim analysis was planned (after 130 events) and why these 3 "safety reviews" were not considered as interim analyses.

The CHMP found it problematic that the study had been stopped so early and that the final PFS analysis did not account for the 3 data looks by the DMC. Only one (later) interim analysis was pre-specified. When accounting for these additional "safety reviews", the p-value did not cross the efficacy boundary (p-value: 0.000104). The observed medians and the HR were estimated based on data from a study that was terminated at a very early stage. It is well-known that such estimates may overestimate the true treatment effect.

However, it has been documented that the hazard ratios were relatively consistent through all DMC safety reviews and similar to the result in the final analysis. It was also acknowledged that a dramatic overestimation of the true treatment effect was highly unlikely.

Updated OS data as of 01 December 2009 demonstrate a persistent advantage for sunitinib on OS, with a HR for OS of 0.594 (95% CI: 0.340, 1.038; p=0.0644, 51 OS events), despite the greater potential for confounding of the OS analysis due to treatment crossover. Mature OS data will be submitted as a FUM, agreed by the MAH, by 31 December 2014, 5 years after LSFV in the pivotal study.

The CHMP considered reasonably well documented that sunitinib has a clinically relevant treatment effect in the proposed indication, although the true benefit may be slightly more modest than in the early presented estimate.

There were concerns due to the limited number of treatment- naïve patients included in the study. The MAH committed to propose and conduct a clinical study to obtain further evidence supporting the efficacy of sunitinib in an adequate number of systemic-treatment-naïve patients as FUM.

Risks

In the pivotal Study A6181111, the following AEs were more commonly reported in subjects on the sunitinib arm as compared to the placebo: diarrhoea, nausea, hair colour changes, neutropenia, hypertension, palmar-plantar erythrodysaesthesia syndrome, stomatitis, dysgeusia, epistaxis, rash, and thrombocytopenia.

Grade 3/4 AEs and treatment-related SAEs, particularly gastrointestinal disorders, were also more commonly reported in subjects receiving sunitinib compared to placebo, although at a modestly increased rate.

Eighteen subjects (21.7%) on the sunitinib arm and 14 (17.1%) subject on the placebo arm were permanently discontinued from Study A6181111 due to a treatment-related SAE, and only 1 subject on each treatment arm had a Grade 5 SAE (cardiac failure on sunitinib; dehydration on placebo) that was considered to be treatment-related, as the majority of SAEs and deaths were related to underlying disease.

Overall, the observed pattern of adverse events was consistent across all 4 studies and with the known safety profile for sunitinib.

Data are consistent with those that have previously been reported with sunitinib, and no new or increased safety risks were identified. Therefore, we can conclude that sunitinib 37.5 mg on a CDD schedule has an acceptable safety profile for the treatment of pancreatic NET.

- Uncertainty in the knowledge about the unfavourable effects

Long-term safety data are not available in the proposed indication due to the premature termination of the pivotal. However, it does not seem to be a major concern as the safety profile of sunitinib has been well-described in other indications and as no new safety signals have been identified.

Safety update from the two open-label extension studies have been provided and also included more mature OS data and AEs of special interest for this type of medicinal product and this indication. No major concerns have been raised on the basis of this safety update.

Benefit-risk balance

Treatment with sunitinib as a 37.5 mg CDD in patients with well-differentiated neuroendocrine carcinoma of the pancreas was associated with a positive effect on PFS without important deterioration in the QoL of patients. These are important clinical benefits in the context of the existing unmet need for this patient population.

Although the early termination of the pivotal study complicated the interpretation of the study results looking at the totality of the data, an important overestimation of the beneficial effects seems unlikely. The safety profile of sunitinib is well-described and common AEs are considered manageable. No new safety signals have been identified. The benefit of sunitinib in the above mentioned indication is considered to overcome the risk associated with the safety profile of the medicinal product.

In conclusion, the CHMP considered that the benefit/risk balance of sunitinib is positive in the following therapeutic indication

"SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

Experience with SUTENT as first-line treatment is limited (see section 5.1)."

Tarceva (erlotinib), to extend the therapeutic indication to include maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of standard platinum-based first-line chemotherapy.

Benefit-risk assessment

Overall Discussion and Benefit-Risk assessment

In the full analysis set, erlotinib was associated with a statistically significant improvement in the primary endpoint PFS (HR=0.71, 95% CI: 0.62, 0.82, p<0.001).

Concerning secondary efficacy endpoints, erlotinib was also associated with an improvement in OS

(HR: 0.81, 95% CI: 0.70, 0.95; p= 0.0088), however no improvement in quality of life or cancer related symptom control was reported.

In line with the advice of the SAG-Oncology, the CHMP concluded that the benefit in terms of PFS and OS was considered marginal and, as it was not supported by an improvement in quality of life or

cancer related symptom control, and did not outweigh the risks associated with treatment. The evaluation of the adverse events experienced by patients confirmed that patients treated with erlotinib presented a statistically significant higher incidence (compared with placebo) of adverse events, serious adverse events an adverse events leading to withdrawal, with diarrhoea, rash and infections being the most frequent side effects reported in a significant part of the population. Thus, the CHMP requested the applicant to try to identify a restricted population for whom the benefit-risk balance could be considered favourable with a clinically relevant effect in terms of important clinical efficacy endpoints.

Following the SAG recommendations the CHMP assessed the subgroup of patients with EGFR activating mutations. In this subgroup the effect in terms of PFS associated with erlotinib administration (HR 0.23, 95% CI 0.12, 0.45, p<0.0001, median PFS 13.0 weeks with placebo versus 46.1 weeks with erlotinib) was very large. However, this analysis was based on too few patients to draw any firm conclusion.

In a subgroup of patients with stable disease it was observed based on post hoc analysis that the treatment effect was larger (HR for PFS 0.68, 95% CI 0.56; 0.83, p<0.0001 and HR for OS 0.72, 95% CI: 0.59; 0.89; p=0.0019). Albeit based on post-hoc analyses of a secondary endpoint, the effect observed in the subgroup of patients with SD at baseline was considered of clinical relevance in this patient population with a generally poor prognosis. The treatment effect was consistent across strata and endpoints, and no important imbalances have been identified that could have biased the study results. In addition, the frequency and intensity of AEs observed for the SD population was in line with the AE results observed in the overall population.

Therefore, the CHMP considered that the Benefit-Risk ratio of erlotinib for the restricted indication as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease following 4 cycles of standard platinum-based first-line chemotherapy is positive.

Tasigna (nilotinib), to include the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myelogenous leukaemia in the chronic phase.

Benefit-risk assessment

Benefits

- Beneficial effects

The efficacy and safety of nilotinib in newly diagnosed patients with CML-CP have been evaluated in a phase III, multi-center randomized, open-label study comparing two different doses of nilotinib (300 mg bid and 400 mg bid) with imatinib 400 mg q.d. (Study CAMN107A2303). Patients were randomized 1:1:1 to nilotinib 300 mg bid. (282 patients), nilotinib 400 mg bid (281 patients) or imatinib 400 mg q.d. (283 patients).

MMR rate at 12 months was doubled in both nilotinib arms in comparison to imatinib. There was no difference in MMR rate for the two doses of nilotinib. Consistent superiority was also demonstrated for secondary endpoints regarding cytogenetic response (CCyR, MCyR). Furthermore, significantly more patients progressed to AP/BC in the imatinib arm (n=11) than in both nilotinib arms (n=3) in the 12 month analysis.

These results indicate higher efficacy for nilotinib compared to imatinib. The response observed in terms of MMR rate and secondary endpoints is expected to result in a clinically relevant effect in terms of relevant long-term clinical endpoints.

- Uncertainty in the knowledge about the beneficial effects.

Overall 7-year survival for patients with newly diagnosed CML treated with imatinib is now 86%, therefore MMR is the only realistic primary endpoint. For patients achieving MMR the 7-year survival is close to 92% and the freedom from progression to AP/BC rate at 7-years is above 95%. Therefore, the long-term efficacy of nilotinib as compared to imatinib cannot be reliably assessed for many years. However, OS needs to be provided post approval on a yearly basis.

Another uncertainty is whether the selected first-line dose of nilotinib 300 mg BID may be inferior in terms of long-term efficacy as compared to the currently approved second-line dose of 400 mg BID. Thus far, there is no indication that efficacy as measured by MMR or CCyR is impaired by the lower dose of nilotinib. However, the dose issue needs to be revisited when 24 months data become available.

Risks

- Unfavourable effects

The observed safety profile for imatinib and nilotinib in the pivotal study was consistent with the known safety profile for both compounds. There were no new or unexpected major findings. The risk profiles of nilotinib and imatinib differ but are overall well known and, with exception of a significant trend for hyperlipidemia in particular hypercholesterinemia, no new safety signals were observed in the pivotal trial. Overall, nilotinib's hepatotoxicity and QT prolongation are the most important risk but seemed to be manageable provided the contraindications and warnings are followed. In conclusion, the safety profile of nilotinib 300 mg b.i.d. is different to but not worse than that of imatinib and is acceptable in the intended indication. It appears more favourable than for nilotinib 400 mg b.i.d.

The MAH is however asked to provide further discussion on the dose recommendation and also to commit to provide long term safety data on key safety issues.

- Uncertainty in the knowledge about the unfavourable effects

Currently only 12 months safety data are available. However, data for the key secondary endpoint will be available after 24 months. This will be submitted in the first quarter of 2011 as committed by the MAH.

Data on the frequency, types and time course of development of nilotinib resistant BCR/ABL mutations, in particular of the TKI- multiresistant mutation T315I may be helpful, however are very limited. At least it could be concluded that at the time being no single case of T315I mutation was identified.

Nilotinib as well as dasatinib are known to be effective in patients with BCR-ABL+ CML that have relapsed after prior use of imatinib. However, the efficacy of treatment when used after refractoriness to or relapse after nilotinib is yet unknown. The MAH committed to make proposals to prospectively collect response data (type, magnitude and duration) in patients receiving second line therapy after relapse or disease progression with nilotinib.

Benefit-risk balance

The higher MMR and CCyR at 12 months achieved with nilotinib as compared to imatinib for first-line use establishes the efficacy of nilotinib in this indication but longer follow-up is needed for conclusive results on the rate of progression to AC/BC and on overall survival.

The observed safety profile for nilotinib in the pivotal study was consistent with the known safety profile. There are so far no indications that nilotinib has any detrimental effects on OS as compared to

imatinib. The safety was better for nilotinib 300 mg BID as compared to the currently approved dose of 400 mg BID. A small difference in QT prolonging effect in favour of imatinib needs careful monitoring including regular OS updates.

In conclusion, in view of the convincing efficacy data and no major concerns in terms of clinical safety, the benefit-risk balance is considered to be positive.

- Discussion on the benefit-risk balance

Exhaustive clinical trial data were submitted to establish the efficacy of nilotinib based on 12 month data on MMR and other secondary endpoints. Although long-term data are lacking, the level of evidence presented is sufficient to expect that the effects observed at 12 months should result in a clinically relevant effect in terms of relevant long-term clinical endpoints.

The data submitted provide adequate reassurance for the efficacious and safe use of nilotinib in the first line treatment of chronic CML. It is considered acceptable that long-term data is submitted as a post-authorisation commitment.

In conclusion, in view of the convincing efficacy data and no major concerns in terms of clinical safety, the benefit-risk balance is considered to be positive.

Taxotere (docetaxel), to include adjuvant treatment, in combination with doxorubicin and cyclophosphamide, of patients with operable node-negative breast cancer eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

Benefit-Risk Balance

The present application is supported by one pivotal, non-blinded, randomized, Phase III study (GEICAM 9805 /TAX.ES1.301), designed to compare DFS (disease-free survival) after adjuvant chemotherapy following primary surgery for breast cancer in high-risk node-negative patients receiving one of the following adjuvant combination chemotherapy regimens:

- TAC (Taxotere, doxorubicin, and cyclophosphamide),

- FAC (5-fluorouracil, doxorubicin, and cyclophosphamide).

In breast cancer adjuvant setting, surgery could result in a cure of the malignant disease. However, many patients will relapse and can die from their cancer. This is related to silent residual diseases/micrometastases not eliminated by surgery. This silent disease in relation to the removed tumour can be local or distant (metastases).

An adjuvant medical treatment is expected to suppress or eliminate this undetectable residual disease avoiding (or delaying) relapses. This delay in relapses is per se a clinical benefit since it provides a prolonged time free from toxic treatments and major health concerns to the patients.

Nevertheless, the benefit of an adjuvant therapy is directly related to the risk of relapse and patients in whom a relapse is unlikely should not have proposed chemotherapy whereas patients at high risk of relapse may be the ideal target of this treatment.

The adjuvant treatment selection algorithm for the management of early breast cancer radically changed during the last decade. As a consequence, and according to the most recent concepts, the benefit of adjuvant chemotherapy is clear for triple negative patients and for HER2 positive disease. For the latter, chemotherapy is given with or preceding Herceptin. For patients with ER positive, HER2 negative disease, the decision for adjuvant chemotherapy is more difficult.

Benefits

- Beneficial effects

Adjuvant chemotherapy benefit should be demonstrated in terms of DFS translating ultimately into beneficial effect on survival. At least, demonstration of the absence of negative effects on survival is expected.

Data from this multicenter open label randomized trial support the use of docetaxel for the adjuvant treatment of patients with operable node-negative breast cancer eligible to receive chemotherapy. 1060 patients were randomized to receive either TAXOTERE 75 mg/m2 administered 1-hour after doxorubicin 50 mg/m2 and cyclophosphamide 500 mg/m2 (539 patients in TAC arm), or doxorubicin 50 mg/m2 followed by fluorouracil 500 mg/m2 and cyclophosphamide 500 mg/m2 (521 patients in FAC arm), as adjuvant treatment of operable node negative breast cancer patients with high risk of relapse according to 1998 St. Gallen criteria (tumour size >2cm and/or negative ER and PR and/or high histological/nuclear grade (grade 2 to 3) and/or age <35 years). Median duration of follow-up was 77 months. Significantly longer disease-free survival for the TAC arm compared to the FAC arm was observed. TAC-treated patients had a 32% reduction in the risk of relapse compared to those treated with FAC (hazard ratio = 0.68, 95% CI (0.49-0.93), p = 0.01). Overall survival (OS) was also longer in the TAC arm with TAC-treated patients having a 24% reduction in the risk of death compared to FAC (hazard ratio = 0.76, 95% CI (0.46-1.26, p = 0.29). However, the distribution of OS was not significantly different between the 2 groups.

- Uncertainty in the knowledge about the beneficial effects

A total of 4 unplanned interim efficacy analyses were performed. The CHMP was concerned that the single pivotal trial for this application may lack robustness and the final statistical significance of the proposed conclusion may not be convincing. Although the methodological weaknesses were acknowledged, the CHMP concluded that in view of the supportive evidence and the overall coherent results, this did not constitute a major issue.

According to the most recent clinical standards (St Gallen 2009 conference), one part of the population included in study GEICAM 9805 would not be treated at all today with adjuvant chemotherapy. Until further data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

OS data are still premature. As a preliminary assessment it can, however, be stated that TAC is a least not worse than FAC in terms of OS. The MAH committed to submit mature OS data as soon as this becomes available.

Risks

- Unfavourable effects

TAC regimen was authorised for the adjuvant treatment of patients with operable node- positive breast cancer in 2004. This indication is based on a single pivotal phase III study, TAX316. The safety profile of docetaxel associated with AC is as expected. However in comparison with FAC, TAC safety profile is expected to be worse in terms of haematotoxicity, cardiotoxicity, colitis, and leukaemia.

Regarding study GEICAM 9805 in the adjuvant treatment of patients with node negative breast cancer, overall, docetaxel in combination with doxorubicin and cyclophosphamide is more toxic than the FAC regimen particularly regarding haematotoxicity.

Haematological TEAEs were more frequent in the TAC group (anaemia, thrombocytopenia, neutropenia, and febrile neutropenia).

Systematic use of G-CSF in the group TAC reduced occurrence of neutropenic events. However, incidence of neutropenia, febrile neutropenia and neutropenic infection remains higher in the TAC group compared to the FAC group (44.9% vs. 13.3%; 9.6% vs. 2.3% and 6.6% vs. 2.7% respectively).

- Uncertainty in the knowledge about the unfavourable effects

Concerning the pre-clinical assessment, several issues regarding the Environmental Risk Assessment, remain. Therefore, a commitment from the MAH to report in due dates the responses to the additional questions, is necessary.

On a clinical view, despite obvious risk of cardiac toxicity due to associated anthracycline in the TAC regimen and potential decrease in LVEF with docetaxel, the study protocol was amended in order to not detect asymptomatic cardiac dysfunctions. This protocol amendment remains not comprehensible and should have been justified. However, the risk of cardiotoxicity is addressed in the proposed SPC for this variation.

When second primary malignancies occurred prior to Breast Cancer Relapse (BCR), they were reported as DFS events. The number of Second Primary Malignancies (SPM) reported as events in terms of the primary endpoint was higher in the FAC group in comparison to the TAC group. Given the high haematotoxicity of the TAC regimen requiring the use of G-CSF, the risk of delayed myelodysplasia and or myeloid leukaemia should be monitored.

Currently there is a trend to an improved OS, the uncertainties for this endpoint, resulting from the large 95%-CIs and the low number of events observed, however, are large.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The CHMP questioned whether the selection criteria in this study correspond to a population that could be expected to benefit from an adjuvant chemotherapy. Indeed, according to recent clinical recommendation (Goldhirsch et al., 2009) one part of the population recruited in the pivotal trial would not be treated at all with adjuvant chemotherapy. The adjuvant treatment selection algorithm for the management of early breast cancer radically changed during the last decade. As a consequence and according to the most recent concepts, the benefit of adjuvant chemotherapy is clear for triple negative patients and for HER2 positive disease. For the latter, chemotherapy is given with or preceding Herceptin. Patients with ER positive, HER2 negative disease constitute a group for whom the decision for adjuvant chemotherapy is most difficult. Patients with small primary tumours (pT1a pN0 and ER negative) might avoid adjuvant systemic therapy. There is no agreement on a standard chemotherapy regimen for any disease subset. Until conclusive data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to the most recent internationally established criteria for primary therapy of early breast cancer.

The CHMP considered that the benefit-risk balance of TAC in the adjuvant treatment of patients with operable node negative breast cancer eligible to receive chemotherapy according to current clinical guidance is positive. Until further data become available, adjuvant treatment should be restricted to patients eligible to receive chemotherapy according to internationally established criteria for primary therapy of early breast cancer.

Tyverb (lapatinib) to extend the therapeutic indication to include the treatment of patients with breast cancer whose tumours overexpress HER2 (ErbB2), in combination with an aromatase inhibitor in postmenopausal women with hormone receptor-positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

Benefit-risk assessment

Benefits:

In patients with HER 2 positive metastatic disease the treatment of choice is generally chemotherapy in combination treatments that target HER 2. However not all patients are candidates for chemotherapy. In postmenopausal women with hormone receptor and HER 2 positive metastatic breast cancer the combination of letrozole and lapatinib has shown a modest increase in PFS compared to letrozole/placebo. The Hazard Ratio (HR) was 0.71 (0.53, 0.96), p= 0.019. The median PFS in the letrozole/lapatinib group was 35.4 weeks compared to 13.0 weeks. This could however be an overestimation a, estimated from HR it should be rather 5-10 weeks. The effect can be acceptable from a clinical point of view.

- Uncertainties:

Breast cancer treatment has changed from study start and substantially more patients are receiving aromatase inhibitors and trastuzumab as adjuvant treatment. A concern is how the new treatment standard would affect the results of the studied combination. In the study only very few patients have received previous adjuvant therapy with aromatase inhibitors or trastuzumab which are current treatment standard for many patients in the proposed population. Data provided to support the effect of the lapatinib/aromatase inhibitor combination after progression on trastuzumab are only data from other settings and not regarding the combination.

As pointed out by the MAH, use of sequential endocrine/aromatase inhibitor treatment is in many cases endorsed and as aromatase inhibitors are widely used a clinical interpretation of the registration study without clear information in the indication could be that addition of lapatinib to an aromatase inhibitor after progression was studied which is misleading.

Furthermore the population failed on trastuzumab and aromatase inhibitors could be a different population both with regards to prognosis and with regards to receptor status and other biologic markers than the population studied where the majority of patients had failed on tamoxifen or were endocrine naive. Data were provided which showed a consistency in Hazard Ratios in different HR levels.

The pivotal trial provided evidence for the superiority of efficacy in terms of PFS of lapatinib+letrozole against letrozole alone, but the application targeted all the postmenopausal, HR+/HER2+ patients in first line treatment for metastatic disease. However, the combination of chemotherapy with trastuzumab is generally recommended for patients with good performance status, visceral disease, or rapidly progressing tumours (Prat, 2008). In the study the majority of patients received chemotherapy on progression. Therefore, the evidence supporting this application may be considered to respect just one of the possible ways of treating the target population of patients. There are no direct data to compare lapatinib+letrozole against combination chemotherapy with trastuzumab.

The combination of trastuzumab and an aromatase inhibitor for the treatment of postmenopausal patients with metastatic breast cancer whose tumours overexpress HER2 is currently approved. To accurately determine the clinical benefit of lapatinib in this context comparisons of lapatinib vs.

trastuzumab, each in combination with an aromatase inhibitor are needed. Data provided refer to phase II-III studies investigating the effect of lapatinib in combination with antihormonal treatment in neodadjuvant and metastatic setting. No studies in either setting were comparing the effect of lapatinib and letrozole in combination with an aromatase inhibitor.

The MAH is now planning for further clinical trials in the endocrine setting with patients pretreated with trastuzumab.

The endpoint PFS is liable to bias, the assessment of the exact magnitude of the efficacy of the combination required a clarification of radiologically versus symptomatically assessed patients. Data and sensitivity analyses showed that it is admissible that despite the imbalance between the numbers of patients with symptomatic progression, the difference is maintained.

No statistically significant difference was seen in the OS, but the data are immature and results may be further diluted after prolonged follow up and use of next-line therapies. Even though currently available survival data are considered reassuring, an update is asked for.

Risks:

The combination of letrozole/lapatinib revealed no new safety signals of importance compared to what was known previously. However the high frequency of grade 1-2 diarrhoea and rash is clearly a concern from a tolerability perspective.

The most common serious adverse events were decreased ejection fraction and diarrhoea; however, the event rates were sufficiently low to be seen as acceptable in the context of treatment of metastatic breast cancer.

Nevertheless, cardiac, hepatobiliary, and pulmonary events, although relatively rare, are matters of concern due to the potential seriousness, warranting continuous monitoring and risk-management measures to allow the detection of a pre-existent deficit predisposing to premature adverse events (case of the cardiac toxicity), or the early diagnosis of toxicity manifestations.

No different safety signals were revealed in older patients, which is reassuring with regards to the population intended.

Balance:

A modest to moderate effect in terms of PFS prolongation has been shown. In individual patients tolerability problems led to discontinuation of therapy. The difference in adverse drug reactions associated with the combination consisted mainly in drug reactions of mild or moderate severity and is not considered to outweigh the benefits observed. In conclusion, the benefit – risk ratio is considered favourable.

Rheumatology, Respiratory, Gastroenterology and Immunology

RoActemra (tocilizumab) to extend the therapeutic indication to include a statement that RoActmera has been shown to reduce the rate of progression of joint damage and to improve physical function, when given in combination with methotrexate.

Benefit-risk assessment

The MAH has provided sufficient data to support the proposed changes to the SPC, especially to include a statement in section 4.1 of the SmPC that RoActemra has been shown to slow progression of joint

damage and to improve physical function. The MAH was asked to change Section 4.1 of the SmPC from "RoActemra has been shown to inhibit progression of joint damage…." to "RoActemra has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate."

This statement is based on one and 2 year x-ray data assessment, assessment of the change in HAQDL and facilitated by other patient reported outcomes as FACIT-fatigue and SF-36 physical function scores. Treatment with TCZ 8 mg/kg + MTX resulted in a 74% inhibition of progression of joint damage compared to placebo + MTX, as indicated by the mean change in total Sharp-Genant score from baseline to week 52. This inhibition was maintained (≥ 81%, from baseline) to week 104.

Patients treated with TCZ 8 mg/kg + MTX had a significant improvement in physical function at week 52 compared with placebo + MTX, as indicated by the AUC of the change in HAQ-DI, and this was maintained until week 104.

Treatment effects in signs and symptoms achieved at year 1 following treatment with TCZ 8 mg/kg + MTX were maintained (ACR50 and 70 responses) or showed further improvement (tender and swollen joint counts) at year 2. Response rates to therapy with TCZ 8 mg/kg (with or without concomitant DMARD) were maintained or improved with duration of treatment (ACR50, ACR70 and DAS28 remission) over time.

In the MAA, identified risks with TCZ treatment were serious infections (including opportunistic infections and infections with possibly fatal outcome), serious hypersensitivity reactions, and complications of diverticulitis, including lower gastrointestinal perforation. Potential risks with TCZ treatment were identified with regard to neutropenia, thrombocytopenia, elevations in hepatic transaminases and lipid parameters, and immunogenicity.

The overall rate of serious infections in TCZ-treated patients (4.66 per 100 patient-years) and the highest rates observed in the All Control population (TCZ 8 mg/kg, 4.9 per 100 patient-years) were both within the rates reported in the literature for other biologic treatments for RA (5.32 per 100 patient-years. The serious infection rate remained stable over time and the pattern of serious infections was consistent with that reported previously.

Serious infections occurred at a higher rate in patients > 65 years of age, patients in the higher weight and highest and lowest BMI categories, patients with prior co-morbidities that predispose them to infections (diabetes, chronic pulmonary disease), patients who previously received anti-TNFs and patients taking background corticosteroids; the highest rates were observed in the TCZ 8 mg/kg group. In general Tocilizumab was well tolerated and the safety aspects were comprehensively characterized by the MAH. Given the nature of RA and the treatments available this product has an adequate safety profile with no reasons for concerns so far over a treatment period of longer than 2 years.

Overall, adverse effects associated with the mechanism of IL-6R inhibition (increased infections, neutropenia) were observed in all TCZ treatment groups. Additional safety aspects (gastrointestinal disorders, skin disorders, increases of hepatic transaminases, platelet decreases, increases in lipids) show a slight higher proportion in the 8mg/kg dosing regimen compared to the 4 mg/kg regimen.

These aspects are adequately addressed in the proposed SmPC.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activity was required: The MAH will conduct study ML25243to elucidate mechanism of reductions in neutrophil count.

Orencia (abatacept), to include treatment of moderate to severe active rheumatoid arthritis in patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF alfa inhibitor.

Benefit-risk assessment

Benefits

The treatment paradigm of RA is changing towards more aggressive early intervention in order to quench the inflammation that may lead to irreversible joint damage and impaired function. Even in aggressive, erosive RA, it is possible to obtain a remission, not only relieve signs and symptoms. Results of the combination therapies, either with traditional DMARDs or with MTX + biologicals, such as abatacept, are significantly better than mono therapy with traditional DMARDs, including MTX. Study IM101023 demonstrated that abatacept + MTX provides a clinically significant benefit to patients with early RA in terms of disease activity, progression of the disease, physical function and quality of life as compared to placebo + MTX. These results are in line with previous studies in advanced RA. The clinical benefit of abatacept appears to be of a similar magnitude as that provided by etanercept, infliximab and adalimumab. Data on the long term benefits of biologicals are scarce and difficult to evaluate.

- Uncertainty in the knowledge about the beneficial effects

The size of the radiological abatacept treatment effect, as measured by a validated clinical score, appeared, however, modest, although the statistical analysis on this outcome was not sensitive to the choice of the analyses method. Across-study comparisons are difficult in this area.

Risks

The tolerability of the combinations that include a biological medicinal product has been relatively good. The safety profile of the combinations with infliximab, adalimumab and etanercept is well known. The most significant serious adverse effects are related to immunosuppression/host defence and include opportunistic infections, lymphomas and various autoimmune disorders. The concerns on the long term safety of abatacept, such as risk of malignancies and autoimmune disorders, are more based on the novelty of the mode of action of abatacept and isolated clinical findings than on real reports of adverse effects in patients. Infections remain the primary identified risk associated with the use of abatacept also during the long term. The incidence rate of infections did not, however, increase over time and serious and opportunistic infections were rare. Data on the long term use of abatacept did not suggest that the risk of malignancies as specifically increased and the rates remained stable over time. Thus, abatacept may offer a relative safety benefit to patients who are susceptible for infections as compared to TNF-inhibitors. Confirmation on this point may come from the ongoing pharmacoepidemiological studies.

Because of these concerns, a robust risk management program was established for abatacept at the time of licensing. This extensive risk management program for abatacept links several registries, post marketing and clinical trial experience. The majority of these patients were enrolled after an insufficient response to one or more non biologic DMARDs including MTX. During the cumulative period, 1280 patients had an inadequate response to MTX, 1419 patients having previously failed one or more anti- TNF agents, and 483 patients were MTX-naive. Since its initial approval in the EU with the abatacept indication limited to the anti-TNF failure population (third line indication), additional safety data has been collected from the long term extensions of the clinical trials, the established RA registries, and the post-marketing experience, totalling an exposure of approximately 73,882

patientyears (p-y) of exposure (11,657 p-y cumulative trial, ~ 2000 p-y from post-marketing epidemiology studies, and ~60,225 p-y post marketing pharmacovigilance). These safety data are not limited to the third line indication as abatacept is marketed in the United States and other countries with an indication for use in MTX-inadequate responders, as well as in MTX-naive patients (over 10000 patients in total).

Overall, abatacept is well tolerated by most patients. No new, unexpected adverse events have been detected in the long term follow up studies, the sole new randomised controlled trial or in post marketing experience. Compared to the original application, the identified and potential risks have also been better characterised over time. The frequency of overall adverse events and serious adverse event did not increase over time.

- Unfavourable effects

Infections remain the primary identified risk associated with the use of abatacept also during the long term. The other concerns on the long term safety of abatacept, such as risk of malignancies and autoimmune disorders, are based on isolated clinical findings and novelty of the mechanism of action.

- Uncertainty in the knowledge about the unfavourable effects

Abatacept has a comprehensive risk management plan that consists of extensions of clinical trials, pharmacoepidemiological study based of several RA registers as well as immunological studies and standard post-marketing safety surveillance. It is unfortunate, that data from the epidemiology/ registry studies in the RMP are not yet able to provide more definite answers to the different safety concerns in early RA. The full planned analysis of the pharmacoepidemiological data across the registries is not expected to start before 2011. The current extracted data are interim in nature and mainly from unadjusted analysis. As outlined in the RMP, once there are 5000 p-y across all studies, these analyses will be performed, but these data will available at the earliest 2011. Currently the exposure is approximately 2000 p-y of follow-up. Keeping these limitations in mind, when comparing key events between abatacept and control groups, the results appear reassuring. The current data do not raise any new safety signals.

Benefit-risk balance

Clinically significant benefits of abatacept have been demonstrated both in early and advanced RA. As discussed above, the mode of action of abatacept raises some potential risks. Against this background, the RMP has a paramount role in the ongoing safety monitoring of abatacept. The risk management system is extensive and on the basis of the current know safety data, with no clear new safety signals, it is considered adequate (with an update on post treatment follow-up of immunogenicity), also for the detection of rare events and events with latency, provided that the exposure and recruitment to the pharmacoepidemiological programme is adequate.

- Discussion on the benefit-risk assessment

It is generally accepted that the combination of MTX with a biological is more active than methotrexate (MTX) alone and this appears true also for the abatacept-MTX combination. It is acknowledged that the study submitted in this application in support of the initially claimed indication in the MTX naïve population has provided data on clinically significant short term benefits. It can be seen that the different trials in early RA (abatacept and anti-TNF) are also similar in their design and results. The size of the radiological abatacept treatment effect appeared, however, small and comparisons to other therapies cannot be fully estimated on the basis of this submission, which would argue against the use of abatacept as first-line monotherapy. In the absence of a head-to-head comparison to a TNF inhibitor, there is some uncertainty of the relative benefits as compared to TNF inhibitors. For the time

being, the safety data have not revealed clear safety signals other than increased susceptibility to infections. On the basis of a quite sizable safety data base, abatacept appears to lack some adverse effects associated with TNF-inhibitors. Thus, the relative benefit/risk of abatacept and TNF-inhibitors, especially in the long term, remains somewhat uncertain. Therefore, an application for a first line indication (or the use of abatacept as monotherapy in case of methotrexate intolerance) is considered premature, which was accepted by the MAH.

However, based on the available evidence and particularly the safety data generated since the original licensure the CHMP recommends that abatacept is placed into the second line for patients who have responded inadequately to one or more DMARDs or TNF-inhibitors. In these patients, the benefits outweigh the potential risks. Hence, the proposed therapeutic indication is as follows: "ORENCIA in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonist.