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GUIDELINE ON THE CLINICAL EVALUATION OF MEDICINAL PRODUCTS INTENDED FOR TREATMENT OF HEPATITIS B

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GUIDELINE ON THE CLINICAL EVALUATION OF MEDICINAL PRODUCTS INTENDED FOR TREATMENT OF CHRONIC HEPATITIS B

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EXECUTIVE SUMMARY

This Guideline is intended to provide guidance for the evaluation of new medicinal products in chronic hepatitis B. This Guideline should be read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Dose-Response Information to Support Drug Registration (ICH E4),
- Statistical Principles for Clinical Trials (ICH E9),
- Choice of Control Group in Clinical Trials (ICH E10),
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),
- Note for Guidance on the clinical development of medicinal products for the treatment of HIV infection (CHMP/EWP/633/02),
- Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99),
- CHMP Points to Consider on non-inferiority margins (CHMP/EWP/2158/99).

1. INTRODUCTION (background)

This Guideline is intended to assist applicants during the clinical development of antiviral products for the treatment of chronic hepatitis B. It is focused on treatment of chronic hepatitis B and not on prevention. The discussion will take into account recent documents that have been issued by learned societies in the field of infectious diseases and clinical virology and recent applications for marketing authorisation for new antiviral agents against Hepatitis B Virus (HBV). The essential issues in the design of clinical trials for hepatitis B that are covered, include indications for therapy, diagnostic criteria and definitions, use of serological and virological markers and selection of efficacy endpoints for treatment.

Prospects for successful treatment of hepatitis B infection have improved substantially during the last decade due to the development of new anti-HBV drugs and to advances in our understanding of viral replication and pathogenesis. However, current therapy of chronic hepatitis B has limited long-term efficacy and potential drawbacks. Existing therapies in Europe include two classes of compounds; recombinant alpha-interferons with antiviral and immunomodulatory effects and nucleos(t)ide analogues with direct antiviral activity. As more anti-HBV drugs with direct antiviral activity such as new nucleo(st)ide analogues become available, the emergence of drug resistance will probably become the most significant obstacle to eventual control of HBV infection. A single drug might never be able to permanently control or to eliminate chronic hepatitis B. Therefore combination therapy might be the most appropriate strategy to develop, which has the potential of additive or synergistic antiviral effects and decreased rate of resistance. Basic research into mechanisms of drug action and interaction should assist in the design and optimisation of combination chemotherapy for HBV infection.

It is recognised that several major issues remain unresolved, such as the optimal treatment of chronic hepatitis B, the use of viral surrogate markers and the role of viral suppression of HBV DNA below the limit of detection of very sensitive PCR assays to prevent disease progression and improve long-term outcome. Moreover, contentious issues remain about defining when antiviral therapy is indicated, whether to treat for a defined interval or indefinitely and when to stop treatment if the defined response criteria are not achieved. The resolution of one or more issues may influence the appropriate design and patient selection criteria of clinical studies. Thus, along with this document, note must be taken of current and generally acknowledged treatment guidelines. The influence of any such documents on the content of the clinical development programme should be discussed in the expert reports/clinical overview and also in individual study reports. As the field of drug development for HBV is in an evolving stage, new specific regulatory issues that require to be rapidly implemented may be covered by future amendments to this document.

The global burden of disease of Hepatitis B virus (HBV) is substantial with more than 350 million people infected and contributing to about 1 million deaths annually. The prevalence of HBV varies widely by geographic area, ranging from 0.1-2% in low prevalence areas such as Western Europe to >=8% in the high prevalence areas of South-East Asia and Sub-Saharan Africa. HBV infection is a complex disease entity that may either resolve spontaneously or manifest itself in variety of ways. Chronic carriers of HBV are at increased risk of developing long-term complications, i.e. cirrhosis, hepatic failure and hepatocellular carcinoma (HCC). Between 15-40% of people chronically infected with HBV are expected to develop serious sequelae during their lifetime. Therefore, effective antiviral treatment is an important aspect in the management of chronic hepatitis B and its complications.

Antiviral therapy is, however, not indicated for all patients with chronic hepatitis B infection. The disease has a broad virological and clinical spectrum and several variables must be taken into consideration before a decision to treat is made and therapeutic strategy is chosen. Correct disease staging and categorisation of patients according to the particular phase in the natural history of chronic hepatitis B are crucial to interpret the results of clinical trials. As more information on predictors of response become available, therapies should be designed that are tailored to viral and host factors as well as stage of disease. The role of virological factors such as genotype and viral mutations in the progression of disease and response to therapy need to be considered in the design of trials. The HBeAg negative chronic hepatitis B has been established as a distinct disease entity that requires separate analyses.

The endpoints to assess the treatment response for different treatment regimens have not been standardised. One of the major issues is the value of viral load measurements to assess response to antiviral therapy. Inconsistency in the definition of overall response, lack of standardisation of HBV DNA assays and heterogeneity in patients populations make comparison between different trials difficult. Therefore, clear definitions of efficacy response parameters for virological, histological and biochemical responses must be used to make possible a consistent interpretation of data.

The introduction of nucleos(t)ide analogues against HBV made new definitions of response to therapy in relation to HBeAg and time-points of assessment necessary. In interferon trials loss of HBeAg was identified as an important endpoint indicating long-term improvement of disease, but this endpoint has proved problematic with the new generation of antivirals. Since nucleos(t)ide analogues suppress, rather than eradicate HBV replication, end-of treatment responses, including HBeAg loss, are not predictive of long-term benefit or remission of disease with this class of drugs. Long-term use of these agents as continuous maintenance treatment necessitates definition of appropriate time-points for evaluating and discontinuing therapy. These facts have important implications for the selection of appropriate timepoints for assessment of response and duration of follow-up.

It is recognized that other immunomodulatory therapies, such as so called therapeutic vaccines (immunotherapy), are under development. Since there is only limited experience with these therapies, scientific advice from European regulatory scientific advice is recommended at an early stage in the clinical trial programme.

The recent development of quantitative polymerase chain reaction (PCR) assays has changed the concept of non-replicative infection and offer better tools to monitor response of therapy. The availability of these sensitive assays has raised several important questions, such as the level of viraemia associated with progressive disease, the level of viraemia indicating treatment and the level of viraemia associated with sustained virological response, with HBeAg seroconversion and with remission of liver disease. These issues remain under investigation, but need to be addressed in the design of the trials. The value of viral kinetic studies also needs further examination.

The ultimate goal of treatment of chronic hepatitis B is to suppress HBV replication and to induce remission in liver disease before cirrhosis and HCC develop. Reliable surrogate markers for long-term remission in disease are, however, not firmly established. It is currently unknown if viral eradication or sustained suppression of viral replication is necessary to prevent progression of disease. Moreover, it is not clear if viral clearance is an attainable goal, because of the difficulty in eliminating the covalently closed circular form of HBV DNA (cccDNA) in the liver. Moreover, HBV sanctuaries in biliary, lymphoid and other extra-hepatic tissues have been identified. Novel sensitive quantitative

methods are being developed for detection of cccDNA in liver tissue to study mechanism of persistence, which in the future could be applied for monitoring effects of antiviral therapy.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 Definitions and diagnostic criteria

The most commonly used definition of chronic hepatitis B infection is presence of serum HBsAg for at least 6 months. The outcome of HBV infection is variable, influenced by age at infection, immune response and environmental factors. Chronic hepatitis B in immunocompetent patients typically runs through three potentially successive phases; immunotolerant, immunoactive and low-/non-replicative. The *immune tolerant phase* is characterised by presence of HBeAg, high levels of serum HBV DNA, normal or minimally elevated serum aminotranferases and minimal or no liver necroinflammation on liver biopsy. In the *immunoactive phase*, serum HBV DNA levels decrease and serum aminotranferase levels increase, sometimes manifested by symptomatic flares, usually followed by HBeAg seroconversion to anti-HBe and transition to a *non/low-replicative phase* with remission of disease ("inactive HBsAg carrier state"). Liver biopsy during the immunoactive phase shows mild to severe necroinflammation. In some patients HBeAg seroconversion is accompanied by the selection of HBV variants unable to produce HBeAg, usually because of mutation in the pre-core or core promoter region. A proportion of these HBeAg-negative patients develop progressive HBeAg negative hepatitis with continued or intermittent necroinflammation and presence of substantial HBV DNA replication. The HBeAg negative chronic hepatitis B is established as a distinct disease entity separated from HBeAg positive hepatitis that requires separate analyses although a combined study with pre-planned analyses could be considered acceptable. There are major genotype and geographic variations in the two forms of chronic hepatitis B that also have to be considered in the design of clinical trials.

The evolution of the three phases of HBV disease differs by age and mode of acquisition of HBV and thus, by geographic region, which has implications for the selection of study patients. Because HBV infection produces a variety of disease states, standard definitions are needed. For staging of disease, the following definitions and diagnostic criteria can be recommended for use, according to recent guidelines (reference AASLD, EASL). These definitions rely upon repeat testing over at least a 6-month period.

Definitions:

Chronic hepatitis B

Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Based upon HBeAg status chronic hepatitis B can be subdivided into HBeAg positive chronic hepatitis B and HBeAg negative chronic hepatitis B.

Inactive HBsAg carrier state

Persistent HBV infection of the liver without significant ongoing necroinflammatory disease

Resolved hepatitis B

Previous HBV infection without further viriological, biochemical or histological evidence of active virus infection or disease

Acute exacerbation and flare of hepatitis B

Intermittent elevations of aminotranferase activity to more than 10 times the upper limit of normal and more than twice the baseline value

Reactivation of hepatitis B

Reappearance of active necroinflammatory disease of the liver in a person with a history of inactive HBsAg carrier state or resolved hepatitis B

HBeAg clearance

Loss of HBeAg in a person who was previously HBeAg positive

HBeAg seroconversion

Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative, associated with decrease in serum HBV DNA <100 000 copies/ml*****

HBeAg reversion

Reappearance of HBeAg in a person who was previously HBeAg negative and anti-HBe positive

Decompensated hepatitis B

For example defined by Child-Pugh score >=7 in patients with known cirrhosis

*See section 4.1.1 on viral load

Diagnostic criteria:

Chronic hepatitis B

1. HBsAg positive >6 months
2. High levels of serum HBV DNA (>100 000 copies/ml for HBeAg positive patients and >10 000 copies/ml for HBeAg negative patients)
3. Persistent or intermittent elevation in ALT/AST levels
4. Liver biopsy showing chronic hepatic inflammatory injury (necroinflammatory HAI score ≥4))*****

Inactive HBsAg carrier state

HBsAg positive >6 months

HBeAg negative, anti-HBe positive

Low levels of serum HBV DNA

Persistently normal ALT/AST levels

Liver biopsy showing little or no necroinflammtion (necroinflammatory HAI score <4) (optional)

Resolved hepatitis B

History of acute or chronic hepatitis B or the presence of anti-HBc +/- anti-HBs

HBsAg negative

Undetectable serum HBV DNA (very low levels may be detectable by sensitive PCR assays)

Normal ALT

* Liver biopsy is required until such time as other criteria, e.g. non-invasive markers, have been accepted.

2.2 Indications for therapy and inclusion criteria

The target population according to the claimed indication has to be specified and reflected in the patient selection criteria. All efforts should be made to assure that the trial population is as close as possible to the target population. The inclusion and exclusion criteria should ensure that enrolment is limited to those patients who are in need of anti-HBV therapy. Ultimately, the indication for therapy is dependent on histology activity scores (HAI scores).

The patients to be included in clinical trials i.e. the target populations include:

i) subjects with HBeAg positive chronic hepatitis B with signs of significant disease activity, i.e. moderate to severe chronic hepatitis on biopsy, active virus replication (serum HBV DNA >100 000 copies/ml) and persistent elevation of alanine aminotranferases (ALT) >2 times the upper limit of normal (after at least 6 months of observation).

ii) subjects with HBeAg negative chronic hepatitis B with signs of significant disease activity, i.e. moderate to severe chronic hepatitis on biopsy and active virus replication. A lower serum HBV DNA as the threshold to indicate treatment (HBV DNA >10 000 copies/ml) is considered appropriate for this group. HBeAg negative chronic hepatitis B disease has a heterogeneous course with different patterns of ALT elevations being either continuos,

fluctuating or intermittent and relapsing, and therefore ALT elevation, as an inclusion criterion, may not always be required for this population.

iii) subjects with lower levels of HBV replication (10 000-100 000 copies/ml) and lesser degree of ALT elevation (<2 times the upper limit of normal) who have significant liver disease. In this group of patients, presence of significant liver injury on biopsy constitutes an indication for antiviral treatment.

iv) in subjects with compensated cirrhosis and persistence of HBV DNA

Patients included in confirmatory trials should be well characterised as regards disease stage and type (HBeAg positive and HBeAg negative), duration, activity and complications. Baseline data should include virological, serological, biochemical and histological parameters. Taking into account the fluctuating course of HBV infection, data on testing of ALT, HBV DNA and HBeAg/anti-HBe on more than one occasion over a 6-month period (taken from clinical records or collected prospectively) should be included in the baseline assessment.

The following target populations might be selected for study:

- Immunocompetent patients with moderate to severe liver disease
    - HBe Ag positive
    - HBeAg negative
- Immunosuppressed patients
- Patients with decompensated hepatitis B
- Orthopic Liver Transplant (OLT) patients
- Co-infected patients (HIV; HCV; HDV)
- Patients with drug-resistant HBV

For each indication the range of patient ages, severity of disease and co-morbidity, co-infections and relevant aspects of patient management should be sufficiently broad to cover the spectrum of intended use. Patients with drug-resistant chronic hepatitis B must be characterised by prior antiviral treatment, by virus mutations (genotypic and phenotypic analysis) and HBV DNA level. The documentation of severity of disease with the aid of a well-established histological scoring system, including classification of grade of necroinflammatory activity and stage/extent of fibrosis, is always recommended. Absence of histology measurement must be carefully justified. Subset analysis should be performed by presence or not of cirrhosis. Patients with decompensated liver disease should be categorised according to established clinical scoring systems (Child-Pugh Turcotte score). Clinical studies of patients with dual infections require specific considerations and study designs.

The selected study population should include patients from different geographic regions, as well as men and women in sufficient numbers to allow meaningful subgroup analyses. It is desirable that protocols and data analyses should plan for stratification of patients from the outset according to one or more factors as appropriate to the indication that are most likely to affect outcome (e.g. HBV DNA levels, ALT levels and HAI scores). Currently, risk factors for developing liver disease include older age, male gender, presence of HBeAg, mutations in the pre-core and core promoter regions of the viral genome and co-infection with other hepatitis viruses or HIV. In addition, HBV genotype (A-H) needs to be determined, since recent data suggest that genotype may be related to clinical outcome and that genotype affects response to antiviral therapy.

When safety has been reasonably established in adults and efficacy data are available, clinical trials in the paediatric population need to be performed. Similarly, therapeutic agents against hepatitis B must be expected to be sufficiently safe before frail populations, such as decompensated patients, are enrolled. Safety and efficacy in special populations such as immunosuppressed patients, liver transplant patients and patients co-infected with other hepatitis viruses or HIV should also be studied. As for other medicinal products pharmacokinetic studies should be conducted as appropriate in patients with impaired renal and hepatic function and prospective gathering of safety data in patients with renal insufficiency or hepatic impairment due to non-viral causes is recommended. Until such

time as proper safety and efficacy data are made available in these groups of patients, the Summary of Products Characteristic would carry statements regarding any such deficiencies.

3. METHODS TO ASSESS EFFICACY

3.1 Treatment Responses

The heterogeneity of hepatitis B disease and its slow and variable progression to "real" (long-term) endpoints (liver failure, cirrhosis, HCC and death) together with limitations of available diagnostic technology, make it difficult to define criteria by which the success of different therapeutic strategies can be judged. At present the most appropriate surrogate marker for long-term remission in disease, although not yet fully validated, is HBsAg seroconversion to anti-HBs. Long-term follow-up of patients treated with interferon supports the paradigm that a sustained major suppression of HBV replication particularly if associated with HBeAg seroconversion interrupts the natural history of hepatitis B. With the introduction of nucleos(t)ide analogues, a judgement of efficacy in patients that is primarily based on HBeAg seroconversion is untenable, and the need to redefine treatment goals has become evident with this class of drugs. These objectives include suppression of HBV replication for prolonged periods to the lowest possible levels, temporary or permanent reduction of hepatitis necroinflammatory activity, arrest of fibrotic progression, prevention of cirrhosis and liver failure and prevention of recurrent HBV infection after liver transplantation.

Based on the above, new therapies will be judged and categorised according to their ability to initiate and sustain long-term viral suppression. However, the assessment of histological response is currently considered the most objective efficacy variable as it corresponds to the ultimate goal of therapy, i.e. to induce remission of liver disease. Although recent studies have demonstrated that suppression of viral load corresponds to histological improvement, the mode to use viral surrogate markers and the role of viral eradication to prevent disease progression and long-term outcome still remain to de determined.

3.1.1 Virological response including serological parameters

HBeAg loss

Considering the natural history of chronic hepatitis B, loss of HBeAg with or without acquisition of anti-HBe (i.e. full HBeAg seroconversion) $\geq$6 months after end of therapy was previously used in interferon studies as an endpoint for success of therapy. However, several limitations to using HBeAg loss as an endpoint have been revealed:

- HBeAg loss is not applicable to patients with HBeAg negative disease.
- The significance of HBeAg seroconversion differs between HBV genotypes due to their different propensity to develop pre-core mutants and is not always a reliable marker for long-term improvement in disease (e.g. in patients with genotypes B, C and D).

HBeAg seroconversion has proven a meaningful endpoint in HBeAg positive hepatitis B for therapies with alfa-interferons. With the development of newer nucleos(t)ide analogues with direct antiviral activity, the HBeAg endpoint has proven problematic since its durability is less robust. The timing of assessment of HBeAg loss in these trials has been different from those with interferons, since the response was defined during therapy rather than after therapy. Only limited data are available on the longterm durability of response after cessation of treatment. Thus, HBeAg loss during nucleos(t)ide therapy does not carry the same long-term implications that were identified in initial studies of the natural course of chronic hepatitis B and long-term follow-up studies after interferon therapy. The introduction of nucleos(t)ide analogues in the treatment of HBV infection has made it necessary to define more precise virological endpoints by use of the more sensitive assays for serum HBV DNA for this class of drugs.

Data on the previously used surrogate endpoints of successful treatment, i.e. for HBeAg positive, loss of HBeAg, suppression of HBV DNA to undetectable levels and normalisation of ALT and for HBeAg negative, normalisation of ALT and suppression of HBV DNA to undetectable levels should be provided as secondary endpoints. Achievement of these endpoints does not guarantee long-term

durable improvement of underlying liver disease or favourable long-term prognoses, but could still be of value since these measurements are widely used in clinical practice.

Studies of the degree of viral suppression in patients undergoing HBeAg seroconversion compared with those not achieving HBeAg seroconversion are encouraged**.**

Viral load

Viral load is an important determinant of the natural history of infection and seems to constitute the most appropriate direct measure of efficacy of antiviral agents. Current PCR assays of serum HBV DNA are very sensitive, measuring levels as low as (10)-100-5000 copies/ml compared with non-amplified assays used in previous trials (>100 000 copies/ml). At present, there are too few data to assess the full clinical significance of different levels of HBV DNA at defined timepoints during treatment and at end of treatment. Future research regarding viral kinetics during treatment is strongly recommended. The concordance between the histological and virological outcomes should be evaluated and should be investigated for any demonstrable correlation with the *in vitro* susceptibilities of the baseline and post-baseline viral isolates.

Clinical trials of chronic hepatitis B require the use of PCR assays initially to establish a baseline DNA level and then continued use of PCR assays during antiviral therapy to measure accurately response and viral rebound associated with viral resistance. The use of validated and sensitive assays that meet current standards is essential. Recent establishment by the WHO of an international standard for HBV DNA assays, with a defined concentration expressed in international units (IU), will enable quality control of the PCR assay used.

In most studies ALT and liver histology improve once serum HBV DNA levels are maintained below 10 000 –100 000 copies/ml and suppression to a lower level may not be needed for long-term clinical improvement. A provisional threshold for treatment of 100 000 copies/mL for HBeAg positive and 10,000 copies/ml for HBeAg negative has been proposed, which could be used in clinical trials. The fluctuating course of chronic hepatitis B necessitates serial determinations to ascertain HBV replication status of study patients. The percentage of patients with viral load below the limit of quantification at 24 weeks, 48 weeks or later is an appropriate virological component of the primary combined endpoint. For the present time, different virological secondary endpoints may be defined, such as time averaged change from baseline and proportion of subjects, who achieve viral suppression below pre-defined levels e.g. <1000 copies/ml, <100 000 copies/ml (the limit of detection of unamplified assays) or below the limit of detection of the PCR assay used. The virological endpoint chosen should be carefully justified.

In order to define the relationship between level of viral suppression and viral response, it is recommended that the dynamics of the early response be carefully documented, not only in dose finding studies, but also in confirmatory studies. If level of viral suppression is to be used as a definition of virological response, the time point of measure must be pre-defined and justified. The potential relationship between viral kinetics and sustained response should be explored.

When standardised assays for HBV DNA in the liver and other tissues have been developed, it could be anticipated that these measurements could be used for monitoring and predicting treatment efficacy. Similarly, the possible use of intrahepatic viral cccDNA measurements warrants serious considerations as endpoints. Any data on these parameters are encouraged.

A detailed description of virological characteristics is desirable apart from quantification of HBV DNA levels, also HBV genotype (A-H), and molecular variants (e.g. pre-core and core promoter mutations).

3.1.2 Histological response

Many systems exist for classifying the histological abnormalities associated with viral hepatitis (e.g. Knodell histology activity index (HAI), Metavir score and Ishak score). A requirement of the scoring system is that it allows scoring of necroinflammatory disease activity separately from fibrosis stage. The applicant should justify his choice of scoring system. A local pathologist usually makes the first assessment by grading the severity of necroinflammation and staging of fibrosis to decide whether the patient fulfil entry criteria. A central pathologist should be engaged to subsequently perform expert

primary assessment. Assessment of liver biopsies should be performed by a pathologist who is not aware of the treatment allocation and the time point the biopsy was collected.

In most trials, histological improvement is defined by decrease in HAI score by two points or more. This definition has not, however, been rigorously assessed or correlated with long-term clinical improvement. Furthermore sampling error on liver biopsy and interobserver variability can account for improvements and worsening of HAI scores by two points or more. For statistical analyses of large numbers of patients a two point or more improvement may be adequate. It is recommended that alternate approaches are explored, such as a definition based upon a decrease by proportion of the initial score (e.g. decrease of 50% compared with baseline) or by a pre-determined amount (e.g. 2, 3 or 5 points) or to a pre-determined level that could be considered minimal or benign (e.g. below 3 points). However, worsening of fibrosis (by = >1 point) is considered the most important intermediate endpoint in disease progression. Any worsening of fibrosis should negate histological improvement in necroinflammatory scores. Separate analyses should be presented for patients with cirrhosis and those with bridging fibrosis.

Currently, no validated non-invasive markers exist of HBV-related activity and fibrosis. However, these markers may eventually be considered as surrogate markers and substitute for liver biopsy. The use of such tests could be considered in clinical trials provided that the applicant could ensure their validation (i.e. comparative data with biopsy)

Immunohistochemical staining of liver tissue for hepatitis B viral antigens could provide supportive data.

3.1.3 Biochemical response

Detection of elevated levels of liver aminotransferases in serum is regarded as a marker of liver damage. A biochemical response is defined by a fall of ALT levels into the normal range. However, patients with normal ALT levels cannot be evaluated for biochemical response and should be excluded from statistical analyses, but may be evaluated in terms of decrease in ALT levels. The exact definition of a biochemical response needs to accommodate situations when ALT levels fall markedly, but not to completely normal levels or aspartate aminotransferase (AST) levels remain elevated (such as in patients with cirrhosis). Data on the proportion of patients with normalised ALT and time to normalisation of ALT should be presented. Any correlation between baseline ALT and virological response should be explored.

3.2 Efficacy Endpoints in Confirmatory Trials

3.2.1 Primary efficacy endpoint

The primary efficacy variable in clinical trials should be specified *a priori* and related to the effect expected from the study drug. The short-term efficacy markers currently used in clinical trials include virological, histological and biochemical parameters. The recommended definitions of response to these variables are shown in the table below. Due to shortcomings of these variables, lack of generally accepted virological markers and lack of rigorous definitions of response, the primary efficacy endpoint to antiviral therapy of chronic hepatitis B in confirmatory trials should, at present, especially for non-interferon therapy, be a combined endpoint including virological, histological and biochemical responses, and defined as a *combined response*.

A *sustained response* is defined by a sustained virological and biochemical response 6-12 months after cessation of treatment. A *complete response* can be considered achieved with loss of HBsAg and development of antibodies against HBsAg (anti-HBs).

Possible definition of response to antiviral therapy of chronic hepatitis B:

BIOCHEMICAL RESPONSE (BR)

DECREASE OF SERUM ALT TO WITHIN THE NORMAL (OR NEAR NORMAL) RANGE

Virological response (VR)

Loss of HBeAg (with or without seroconversion to anti-HBe) and/or decrease of serum HBV DNA to undetectable levels in non-amplified assays (<100 000 copies /ml) or in PCR assays (<500-20 copies/mL)

Histological response (HR)

Improvements in histological scoring, with decrease in histology activity index of at least two points (by more than or equal to 2 -5 points) without worsening of fibrosis (e.g. by = ≥1 point, or other criteria to be justified) compared to pre-treatment biopsy

Combined response

Biochemical, virological and histological response. The use of a combined endpoint applies both for HBeAg positive and HBeAg negative chronic hepatitis B. However, HBeAg loss is not applicable to patients with HBeAg negative disease, and the primary endpoint for these subjects should include normalisation of ALT, persistent loss of HBV DNA and improvements in histological scoring

Sustained response

Sustained virological and biochemical response 6-12 months after cessation of treatment.

Complete response

Loss of HBsAg and development of anti-HBs with responses in other virological, biochemical and histological parameters

Time to virological failure (secondary failure)

For example defined as increase of HBV DNA by >1 $\log_{10}$ copies/ml from nadir

Since this area is in an evolving stage, the proposed definitions might be reconsidered in the future. In particular, the virological endpoint may need revision with the availability of new sensitive assays for the HBV DNA level. Moreover, the response criteria may not apply to all subpopulations (e.g. decompensated patients (see clinical endpoints 4.6.1)). Any choice of other primary outcome measures in confirmatory studies should be justified (se section 4.1.1, viral load).

The study protocol should include predefined definitions of treatment failures. The virological investigation (including comparisons of pre- and post-therapy susceptibilities of HBV and genotypic analyses) of all patients who are clinical failures is expected. Development of resistance should be closely monitored during the whole clinical trial programme.

3.2.2 Alternative primary efficacy endpoint in exceptional cases

In some circumstances the use of alternative measures of clinical outcome may be appropriate. For example when the agent under study is being used to treat serious and/or life-threatening HBV infections in decompensated patients, the time-weighted average change from baseline in serum HBV

DNA and ALT and times to resolution of specific clinical signs or progression to defined events might be suitable outcome measures. Very occasionally it might be appropriate to designate such alternative measures as primary efficacy variables.

For comparative studies in patients with drug-resistant HBV, an appropriate primary endpoint might be time-weighted average change from baseline in serum HBV DNA as well as median change through out a pre-defined treatment period (e.g. 48 weeks). Genotypic analysis of viral strains during and at viral breakthroughs should be performed to detect any HBV wild type reversions. Secondary endpoints should include median changes in and normalisation of serum ALT levels, rates of HBeAg loss and seroconversion as well as histological changes.

3.3 Secondary Efficacy Endpoints in confirmatory trials

These endpoints will be assessed to check the consistency of the conclusion drawn on the basis of the primary endpoints. The protocol should specify the criteria that should be met in order for a patient to fall into one of these outcome criteria. The secondary endpoints that need to be considered include complementary analyses of the components of the combined endpoint such as time-to-event analyses (e.g. to viral breakthrough, to response, to remission), proportion of patients achieving pre-defined endpoints (e.g. the proportion of patients with HBV DNA reduction to undetectable levels, normalisation of ALT and HBeAg loss or seroconversion), analyses of pre-treatment predictors of

successful response to therapy (e.g. HBV DNA level, HAI scores and ALT levels) and subgroup analyses based on HBV genotypes.

3.4 Timing of therapeutic responses

A clear rationale for the timing of the on-therapy visits, the end-of-treatment (EOT) visit and other post-therapy visits and the total duration of follow-up should be provided in the study protocol. The predictive activity of the comparator may be used for guidance as to the proper duration of the trial. Every effort should be made to obtain follow-up information including virological and biochemical data at each of the planned visits on as many patients as possible, to allow full evaluation of longer-term relapse rate. The study reports should account for all missing data at each visit.

The use of interferon-alpha therapy includes a finite duration of treatment, more durable response and the presumed lack of resistant mutants.

With respect to nucleos(t)ide analogues, the need for clearer definitions of timing of responses has become evident. The response to antiviral therapy should be measured on several occasions both on-treatment, at end-of-treatment and after cessation of treatment and characterised in a hierarchical system of chronological endpoints: *initial*, *end-off-treatment* and *sustained response* (see table). When long-term therapy is used, as for the nucleos(t)ide analogues, an additional on-treatment response category, *maintained response* (virological and biochemical parameters at definite timepoints e.g. 1 year, 2 years, 3 years) should be included; in these cases end-of-treatment response and post-treatment response are not applicable**.** The duration of therapy should be specified in the protocol as well as pre-defined criteria when to evaluate response; in these cases end-off-treatment response and post-treatment response are not applicable in the same way as for immunomodulators such as interferon (see 4.5 follow-up evaluation).

Timing of response to antiviral therapy

On-treatment response:
- *Initial response*
Occurring the first 6 months of starting therapy
- *End-of-treatment response (EOT)*
Present at the conclusion of a defined course of therapy (6 or 12 months or longer)
- *Maintained response (applicable to nucleos(t)ide analogues)*
Still present at last of follow-up in a continuous, prolonged course (i.e. more than 1 year) of therapy
Post-treatment response:
- *Sustained response*
Present 6 or 12 months after stopping therapy

Data on *initial response* measuring rates and magnitude of the first phase reduction in viraemia could be used for comparing antiviral activity between different treatment regimens. Optimally, the early virological response after 4-8 weeks of therapy should also be documented. *EOT responses* measuring rates and magnitude of the second phase reduction in viremia have not proven to be reliable predictors of long-term benefit or remission in disease and cannot serve as the primary endpoint.

A follow-up of 6-12 months is necessary to define a *sustained response* to therapy. Criteria defining a durable response should include a long-term sustained virological and biochemical response and ultimately HBsAg seroconversion to anti-HBs. In the future clearance of cccDNA from the liver may also be included in this endpoint.

3.5 Follow-up evaluation

The follow-up evaluation of response at 6-12 months post-treatment should, in normal cases, comprise the parameters included in the combined primary endpoint (virological. biochemical and histological response, as defined in the table on definitions of response). Currently, it is expected that a baseline

and a follow-up biopsy is performed in confirmatory efficacy trials. The durability of the HBeAg endpoint is shorter for nucleos(t)ide analogues than for interferon and needs to be carefully followed up. For HBeAg negative patients a sustained response should include persistent normalisation of ALT and loss of HBV DNA. In special populations (e.g. decompensated patients) the nature of follow-up response should be adjusted to the endpoint criteria used.

During long-term therapy (i.e. more than a year), as applicable for nucleos(t)ide analogues, liver biopsies in a subset of patients at defined intervals is recommended to confirm a maintained response. The outcome of HBeAg and serum ALT and HBV DNA levels should be followed regularly to reveal any grade of ongoing activity or breakthrough infection.

Appropriate post-marketing long-term follow-up of clinical trials for assessing durability of sustained response and incidence of liver-related complications must be planned and defined at the time of application. Any late post-treatment relapses should be carefully documented. For follow-up on resistance development, see safety section 7.1.2.

For approval of new antiviral agents in the treatment of chronic hepatitis B, optimal treatment duration and timepoint that allows cessation of therapy need to have been at least provisionally defined. Clear criteria for stopping therapy must be laid down and the total duration of sequential follow-up must be carefully justified.

3.6 Clinical response

Clinical response to therapy is difficult to assess in compensated patients due to the asymptomatic course of the disease. Therefore, the assessment of efficacy according to clinical events pertains to specific populations, e.g. decompensated patients. The assessment of clinical outcome should be performed at regular intervals up to the end of therapy and at designated post-therapy visits. The protocol should specify *a priori* a responder in terms of clinically meaningful change in the parameters defining the combined endpoint. Decrease in Child Pugh scores from baseline should be documented according to pre-specified criteria. The study should compare the proportion of patients who achieve the stipulated amount of improvement rather than a change in a score. Effective therapy in patients with decompensated cirrhosis should be reflected in an improved Child Pugh score and obviation of the need for liver transplantation. Laboratory evidence of improvement in defined parameters such as serum bilirubin, PK and serum albumin levels at pre-defined timepoints should be recorded. The median (range) change from baseline of these parameters and proportion of patients with normalised values should be recorded.

Time to disease progression as defined by the occurrence of clinical events e.g. the development of spontaneous bacterial peritonitis, bleeding gastric or oesophageal varices, the development of HCC or liver-related deaths should be carefully documented.

In particular, monitoring for hepatitis flares (elevations of ALT levels to more than 10 times the upper limit of normal and more than twice the baseline value) and clinical symptoms during and after end of treatment should be performed.

3.6.1 *Long-term clinical outcome*

Studies assessing long-term clinical outcome of antiviral treatment are encouraged during the post-approval surveillance period. The incidence of hepatic failure, HCC and liver related deaths should be followed.

4. STRATEGY AND DESIGN OF CLINICAL TRIALS

The mode of action of an anti-HBV agent and the potential mechanisms of viral resistance to it should be well described in the pre-clinical studies. In particular, any potential for virus that is already resistant to other agent(s) to show cross-resistance to the antiviral agent under evaluation should be explored in detail. Exploration of the *in vitro* activity and the non-clinical PK and PD properties of an anti-HBV agent should be conducted to the extent as to provide some indication of the dose regimens that should be explored initially in man.

4.1 In vitro pharmacodynamics

There are several useful models for studying *in vitro* pharmacodynamics. Primary duck hepatocytes either congenitally or acutely infected with duck HBV provide an inexpensive, safe and frequently used alternative to primary cultures of hepatocytes from human. Additionally cell lines derived from human hepatocellular carcinomas, which are stably or transiently transfected with HBV (e.g. the HepG2-derived 2.2.15 cell line may be useful). In the future two novel in vitro expression systems will probably gain general acceptance for large-scale pre-clinical screening of potential anti-HBV drugs. The first uses hepatoblastoma cells stably transfected with HBV, the expression, which is inducible, whereas the second relies on a recombinant HBV-baculovirus vector.

It is expected that the antiviral activity and mechanism(s) of action of the novel agent have been well characterised *in vitro*. In vitro anti-HBV activity and susceptibility profile should be determined in HBV transfected human hepatoma cell lines. Comparative *in vitro* studies with relevant anti-HBV compounds should be performed whenever possible. The novel agent should be tested against different clinical isolates (e.g. different HBV genotypes) and recombinant viruses that express various resistance-associated mutations. Considering the organisation of the HBV genome, with partially overlapping open reading frames, resistance-associated mutations could have unexpected effects on proteins encoded by other gene regions, e.g. mutations in the polymerase gene have the potential to affect the expression and function of HBV surface gene and vice versa. Exploration of the implications of such phenomenon is encouraged

Investigation of genotypic and phenotypic resistance and resistance mechanisms is an essential element of drug development. The choice of assays and assay conditions should be justified. The post-licensing development programme should aim to identify resistance-associated mutations and appropriate breakpoints to be applied to *in vitro* susceptibility test results. Studies investigating replicative capacity ("viral fitness") are also encouraged. Potential cross-resistance to other (similar) antiviral drugs should be investigated. Susceptibility profiles of resistant strains to other anti-HBV drugs should be explored.

Before combination therapy is initiated in man relevant *in vitro* studies should have been performed to study potential interaction between drugs and to assess additive and synergistic effects.

4.2 Early Studies in Man

4.2.1 Pharmacodynamics

It is desirable that the PK/PD relationship should be further explored during both the early and confirmatory clinical studies in infected patients to verify the conclusions drawn from the pre-clinical observations and pharmacokinetic data in healthy volunteers. (As suggested in CHMP/EWP/2655/99, these investigations may constitute sub-studies within larger trials or may be the studies that are specifically designed to address PK/PD relationships.)

It is recommended that the relationship between drug exposure and safety and efficacy is explored also in confirmatory studies e.g. by means of population pharmacokinetics/pharmacodynamics.

4.2.2 Pharmacokinetics

The pharmacokinetics of the novel agent should be evaluated in healthy volunteers and patients with chronic hepatitis B in different stages following the existing guidelines. The pharmacokinetic profile should also be investigated in patients with advanced hepatitis B disease, if the novel compound is intended for decompensated patients. With reference to the paediatric population, see section 6.1. The pharmacokinetic properties should be thoroughly characterised. Possible sources of variability e.g. food interaction, drug-drug interactions, age and gender effects, effects of hepatic and renal impairment should be evaluated whenever relevant.

For compounds undergoing intracellular activation e.g. nucleoside analogues, the pharmacodynamics are governed by the intracelllular pharmacokinetics of the activated compound and sources of variability in the concentrations of the activated compound, such as drug-drug interactions, should be investigated.

Interactions studies should be performed in accordance with existing guidelines, governed by the inherent properties of the new compound.

4.2.3 Exploratory studies

The primary aim of these studies is to provide reliable data on (short-term) anti-HBV activity of the new compound and thus provide the best possible basis for the designs of the confirmatory studies. These studies should be designed to minimise the risk that suboptimal doses are investigated further in long-term confirmatory trials. Data derived from these studies may also provide important bridging pharmacokinetics/pharmacodynamics (PK/PD) documentation.

Monotherapy studies are needed to characterise the relationship between anti-HBV activity and dose/concentration. In the dose ranging studies, a treatment arm with established anti-HBV agents could be included to assist selection of an optimal dose. Appropriate modelling might also provide information on pharmacokinetic markers of importance for efficacy in relation to virus with different degrees of reduced susceptibility *in vitro*. If a range of doses is found to be active and well tolerated, additional comparative studies may be warranted. These should be randomised comparing various doses of the novel agent with an active comparator. The clinical pivotal trials might incorporate more than one dosage arm provided that an acceptable number of patients are treated with the proposed dosage.

Early and repeated determinations of viral load and drug concentrations are recommended and PK/PD modelling may be a useful tool for dose selection.

Dose selection for the phase III confirmatory trials of efficacy should be based on the considerations outlined above and should be preceded by well-planned dose ranging comparative studies. These studies should include patients with the same diagnosis/es based on the same criteria that are to be used in the various phase III studies. Virological suppression and kinetics of response constitute acceptable primary endpoint in these trials. The effects of different dosages on kinetics and rate of HBV DNA suppression using quantitative PCR techniques by selected time-points and safety should be documented. Serological and biochemical responses should also be documented.

Dose-ranging studies on efficacy of the novel agent on various resistant variants should be performed.

4.3 Therapeutic Confirmatory Studies

It is important that studies take into consideration the geographic distribution of different hbv genotypes and also the mode of acquisition. Perinatally acquired hbv infection has a different course and potentially a different response to therapy than infections acquired during adulthood. Male and female sex needs to be sufficiently represented. The applicant should be able to demonstrate that the data on efficacy are applicable throughout the EU.

4.3.1 Randomised controlled trials

Ideally, each indication for the treatment of chronic hepatitis B that is sought should be supported by at least one randomised and double blind trial. Where a combined primary efficacy variable has been defined that includes results of histological studies or of laboratory tests, all the personnel involved should be blinded as to the assigned treatment.

Given the efficacy of approved anti-HBV compounds, the inclusion of a placebo group in long-term clinical trials is hardly acceptable. In patients with advanced liver disease, placebo-controlled trials are not considered ethical. However, for short-term therapy (e.g. interferon-alfa for 6-12 months) and in children with high spontaneous resolution rates a placebo-controlled trial to establish efficacy in immunocompetent patients may be possible and ethically justifiable. It is desirable that placebo-controlled trials should incorporate a third (active treatment) study arm if an established treatment is available, in order to properly assess the comparative efficacy and safety of a new product.

The sample size of the studies should allow for the conduct of meaningful subgroup analyses with respect to known response parameters and to factors that potentially affect outcome such as gender ethnicity and HBV genotype. As appropriate, the design should include stratified enrolment, if a combined study of HBeAg positive and HBeAg negative patients is used.

Each study should be adequately powered to show at least non-inferiority to an acceptable active comparative regimen or superiority to placebo (whenever considered to be possible). For non-inferiority studies the margin of non-inferiority should be selected on a case by case basis and should be carefully justified. Further advice is provided in the CHMP Guideline on the choice of non-inferiority margin (CHMP/EWP/2158/99).

At least one year (if the compound is pre-planned for long-term treatment) is needed to exclude clinically relevant inferiority for compounds assumed to be equally effective, even though it may be possible to show superior anti-HBV effects already after 6 months. The study design and duration should allow adequate assessment of a sustained response and potential effects of withdrawal of treatment i.e. include a 6-12 month period post treatment. It is expected that the duration of the study as determined by efficacy considerations is sufficient also from a safety perspective.

If superiority for the experimental arm is convincingly shown at a medium term, pre-planned analysis in a study arm to run long-term e.g. for safety reasons, this may lead to a need to revise failure criteria in order to protect the rights of study subjects. In a study conducted in treatment-naive patients, for example, and depending on the magnitude of the observed difference in efficacy, it may be appropriate to unblind assignment for all individuals with measurable viral loads.

Alternative study designs (e.g. for liver transplant patients) should be used only exceptionally and must be carefully justified. If well-founded estimates of the numbers of patients that might be recruited in a reasonable timeframe across a sufficient number of trial centres support a conclusion that an adequately powered randomised controlled trial would not be feasible, an alternative study design might be considered. The acceptability of any alternative study design would be assessed on a case by case basis.

Even when enrolment is expected to be limited by patient availability, a randomised controlled trial is always preferable to an uncontrolled study or one that attempts a comparison with external or historical controls. Consideration may be given to employing unbalanced randomisation as a compromise between exposing a sufficient number of patients to the novel agent, while still including an appropriate internal control group.

Combination therapy in treatment-naïve patients

Since monotherapies with nucleos(t)ide analogues appear unlikely to be sufficient in achieving sustained HBV suppression in the vast majority of patients, future research seems to be pre-determined to explore combination therapies. Combination therapy has the potential of additive or synergistic antiviral effects and decreased rate of resistance. Because of the similarities between HBV and HIV infection, experience with HIV therapy provides a rational basis as well as valuable guidelines for developing combination therapy for HBV infection.

The rationale for the choice of drug combinations should be based on results in non-clinical models. Mitochondrial toxicity should be addressed, and data on any additive or synergistic effects in vitro and in animal models of the selected drug combination should be provided. Whenever circumstances permit, clinical studies should compare the combination with both the novel and the second agent alone. Such a study design not only allows for an assessment of any additive and synergistic effect of combining the two drugs, but also facilitates the interpretation of the safety data. Continuing studies of viral dynamics using the quantitative PCR techniques and emergence of (multi)resistant variants will be required to determine which combinations are optimal.

The protocol must specify the criteria under which their use is permissible. In general, the protocols should at least outline the criteria that should be met before adding, discontinuing or amending dose regimens of any additional antiviral agents that may be allowed during the study.

Methodology should be carefully planned in special situations such as when sequential therapy is used.

Study Populations

Results for all populations (intention to treat (ITT), per-protocol (PP) and subpopulations) are to be analysed and should be presented and reviewed for consistency. In studies that aim to demonstrate

non-inferiority between test and reference treatments, the primary analysis for the study should usually be the per protocol analysis, since this may be more sensitive for the detection of differences between groups. For superiority studies the most suitable primary analysis is normally that in an ITT population, defined as all treated patients and with all indeterminate outcomes and withdrawals designated as failures.

Study protocols should pre-define the criteria that should be met by patients in order to be considered clinically evaluable and/or virologically evaluable. Appropriate analyses should also be pre-planned for all designated secondary efficacy variables. All withdrawals from the assigned treatment group must be explained in the study protocol and there should be detailed documentation of clinical and virological findings on the day of withdrawal. Procedures of withdrawal (e.g. tapering schedules, add-on therapy) should be predefined. Monitoring of clinical resistance should take place at baseline, on-treatment and at week 48 (and at pre-defined intervals if long-term therapy is planned) and partial sequencing of isolates should be performed on increases in viral load to predefined levels (e.g. >1 log). If resistance emerges, a pre-specified plan for action and monitoring of these patients should be in place.

4.3.2 Choice of comparator in randomised controlled trials

The choice of comparator depends on the indication, and it is necessary to demonstrate that the new drug is at least as effective as the standard of care, which currently in the majority of cases includes peg-interferon alfa-2a, interferon-alfa, lamivudine or adefovir. Therefore clinical trials aimed at supporting a first line indication should always include comparison with the accepted first line treatment.

The active comparative regimen that is chosen for any one trial must be considered to be the best therapy, or among the optimal available therapies, for the condition being treated in all patients eligible for study. The applicant must justify both the agent and the dose regimen that is employed, taken into account medical opinion and treatment guidelines from appropriate specialist bodies. It is preferable that the comparative agent should be administered at a dose regimen that is licensed in all, or as many as possible EU Member States.

When different treatment durations of the test and comparator agents are used, difficulties might arise. The duration of therapy and timing of response assessment should be carefully justified.

In the future, approaches such as intensification/substitutions adapted to selected populations (e.g. lamivudine naïve and resistant, HIV-coinfected or decompensated patients) can be expected. Study designs may be complex and need to take into account the evolving recommendation in term of therapeutic management. Overall, discussion with EU regulators is advised.

4.3.3 Studies in HBV-therapy experienced patients

If the new anti-HBV drug shows potentially useful activity *in vitro* against resistant strains it is appropriate to evaluate it for the treatment of patients who have already failed therapy with another antiviral drug. These patients may be described as refractory cases and the switch to the new agent maybe referred to as next-line therapy. The aim then of a clinical trial is to demonstrate efficacy following a switch to the new agent. Consideration of the evaluation of the new drug in so-called refractory cases and for the resulting indication for use include: i) the possible reasons for failure, ii) the definition of failure on previous therapy(ies), iii) the specific antiviral drugs that have been tried already and iv) the study design. Failure of a patient to respond to antiviral agents may be due to drug-resistant viral variants or insufficient drug concentrations achieved or maintained in the liver.

Most studies in HBV-therapy experienced patients are conducted in patients with evidence of virological failure on the current regimen. The most commonly used study design involves the substitution of one drug with the novel agent within an existing regimen that will serve as a control regimen. These studies should normally be double blinded. The criteria for enrolment should be specified according to length of previous therapy and HBV viral load and data on in vitro susceptibility by genotyping and phenotyping assays. Patients could be randomised to different dose regimens of the novel agent including the one selected for wild-type HBV to investigate the optimal dosage for these resistant variants. A pre-defined duration of therapy when treatment effect should be

analysed (e.g. at week 24 or 48) should be given. Treatment failure should be pre-determined (e.g. increase of HBV DNA by >1 $\log_{10}$ copies/mL from nadir).

Time to virological failure is an acceptable primary endpoint. The primary endpoint may be the percentage of patients with adequate virological control at e.g. 24 or 48 weeks, but time-averaged difference may be an acceptable alternative. The treatment goal in clinical practice is to achieve a viral load below the limit of quantification, and the proportion of patients that achieve this degree of viral suppression should always be reported

The wording of any indication for use would have to reflect the individual anti-HBV agents that the patients to be enrolled in such a trial had previously received for their ongoing infection.

In patients with multi-resistant strains it might not be possible to conduct controlled trials. Early regulatory advice is recommended, whenever an uncontrolled design is envisaged.

An uncontrolled study should only be selected when there is no possibility of some form of prospective comparison between treatments. Such circumstances might include treatment of patients with infections that have been documented resistant to all other available therapies and/or appear clinically refractory to other established anti-HBV drugs and with advanced liver disease. If an uncontrolled design is chosen, all possible attempts should be made to generate precise and unbiased estimate of efficacy for the new agent in a clearly defined population in order to facilitate the interpretation of data. Occasionally, an uncontrolled study may be used to supplement data obtained from randomised and controlled studies. **In these special circumstances, it is recommended to seek advice from EU regulators.**

4.3.5 Statistical analysis and reporting of the results, with consideration on the expected clinical benefit if relevant**.**

The existing guideline (e.g. E9: Statistical Principles for Clinical Trials) should be followed.

5. STUDIES IN SPECIAL POPULATION

5.1 Paediatric patients

Hepatitis B in childhood differs from that in adults in many ways, i.e. with respect to routes of transmission, rates of chronicity and natural course of disease. Vertical transmission of hepatitis B from mother to child is a major route to establish a chronic carrier state. Infection during infancy and early childhood is acquired by horisontal transmission from child-to-child contact in household settings. In adolescents transmission through sexual activity and intravenous drug use predominate. The risk of chronic hepatitis B infection is inversely related to the age at infection and up to 90% of infants infected in the perinatal period become chronic carriers. In children infected during the first five years of life, the risk of developing chronic infection is around 20-30%, while in older children and adults the risk is below 5%.

Most of the children with chronic hepatitis B are asymptomatic in spite of a high-level viremia, but run a long-term risk of developing cirrhosis or hepatocullular carcinoma later in life. The initial immune-tolerant phase is usually followed by an immune-active phase with increasing ALT and in favourable cases loss of HBeAg and seroconversion to anti-HBe with decreasing level of viremia. Around 40% of children clear HBeAg within one year after the detection of elevated aminotranferases. Most of those children who seroconvert have stable remission with normal ALT. The immune tolerant phase can last for many years, in particular in perinatally infected children. Long-term follow-up studies in Caucasian children have shown that more than 80% seroconvert from HBeAg to anti-HBe before reaching adulthood. Lower figures are reported in Asian children, possibly due to the fact that perinatal transmission is the dominant route of infection in this area. The annual spontaneous HBeAg seroconversion rate in Caucasian children is up to 14-18%, whereas in Asian children below 3 years of age it is less than 2%.

A prolonged immune-active state could indicate a worse course of disease, but at a given time there is currently no biochemical or virological markers that can identify children with a more serious prognosis. The long-term complications of chronic HBV, cirrhosis and HCC, most often develop in adulthood, but cirrhosis and HCC has also been found as an infrequent complication in children.

Considering the natural course of chronic hepatitis B in children with the increased possibility of natural HBeAg seroconversion, the indication for antiviral therapy is different from that in adults. Currently, the target group for antiviral treatment is children with a long-lasting immune active phase with increased ALT more than 2-5 times the upper limit of normal and HBV DNA levels >100 000 copies/ml for more than (6)-12 months. Preferably a baseline liver biopsy should be performed demonstrating moderate to severe necroinflammation. Justification is expected, if other paediatric populations are included in the studies. Study designs may be complex and discussion with EU regulators is advised.

Dose selection in children is often based on the results from pharmacokinetic studies where doses in different age groups are selected to produce blood levels similar to those observed in adults. Considering the different disease characteristics in children and adults, in particular the higher rate of spontaneous remission of chronic HBV disease in children, separate efficacy trials in children are considered necessary. When an active versus placebo design is possible and ethically justified, it should be pursued. Data on the safety and efficacy of the proposed dose regimens over appropriate time spans should be provided. Follow-up should be performed as outlined for adults (see section 4.5). Long-term post-marketing and pharmaco-epidemiological studies are encouraged.

At the time of licensure all relevant information already available in children should be mentioned in the SPC (e.g. in sections 4.8, 5.1 and 5.2) even if there are insufficient data at the time to support a formal indication for use in one or more groups. In these instances the satisfactory completion of investigations in children would be a post-approval commitment and a timetable should be provided.

5.2 Decompensated Cirrhotic Patients including Liver Transplant Patients

Patients have to be characterised by the Child-Pugh scoring system or other validated scoring systems e.g. model for end-stage liver disease (MELD). Specific consideration must be taken of the safety profile of the anti-HBV agent and the potential for emergence of resistance-associated hepatic flares in this frail population. Placebo controlled trials are not considered ethical in this severely ill patient population and an active control comparator medication should be used if available. Currently, studies comparing combination regimen versus monotherapy are encouraged. Since long-term and perhaps even indefinite therapy is a possible treatment approach in these patients, on-therapy monitoring of clinical status and viral load must be performed at defined intervals (e.g. every 3 months) and individualised depending on the risk of decompensation in the event of emergence of resistance. Considering that this population has multiple risk factors for renal impairment, monitoring of renal function before and during long-term therapy is particularly important, and should be pre-planned in the study protocol. Criteria for adjustment of doses at defined Creatinine clearance values should be defined.

Patients enrolled should be well characterised by renal, hepatic and haematological function and if relevant, by previous anti-HBV therapy. Patients should be described and defined by pre- and post-liver transplant status. Any change in immunosuppressive therapy should be carefully recorded during the post transplant period. Liver biopsy might not be possible in patients with advanced liver disease due to impaired clotting function and therefore the primary efficacy endpoint could be defined by virological response (time-weighted average change of HBV DNA from baseline to a pre-defined time-point, e.g. 24 or 48 weeks). Biochemical response, decrease in Child-Pugh score and survival at week 48 should be documented as secondary efficacy endpoints. Patients with signs of breakthrough infections should be well characterised virologically with genotypic analysis. Long-term follow-up in this patient group is strongly recommended for assessing rate of HBV reinfection and emergence of drug-resistant variants, incidence of liver complications and survival rate. Post-marketing studies to evaluate long-term outcome of virological and clinical response should be pre-planned and defined in the study protocol.

5.3 Co-infected patients with HBV and HIV

Specific considerations in the choice of study therapy must be taken in patients, who are co-infected with HBV and HIV, since treatment of HBV infection should not impact negatively on antiretroviral therapy (ART). HIV and HBV co-infected patients whose immune status is preserved or restored on antiretroviral therapy should be considered for anti-HBV therapy. The criteria for therapy, based on

virological, biochemical and histological parameters, for non-HIV infected hepatitis B patients can be extrapolated to co-infected patients. A liver biopsy is highly recommended, since ALT levels may be a less sensitive indicator in this setting. Study patients should be well characterised for both HIV and HBV as regards disease stage, viral load and immune status, including CD4 cell counts.

In the design of these studies specific considerations must be taken regarding anti-HBV drugs that exert activity against HIV, and that initially was approved for HIV and then developed for HBV. Monotherapy studies with such agents in ART-naive HIV-infected cases cannot be performed at doses active against HIV, whereas it is acceptable to give the agent as part of a combination ART regimen. The study protocol should clearly define which of the two diseases that is to be evaluated and efficacy parameters adjusted accordingly. Viral loads of HIV and HBV viruses should be monitored so as to assess any potential for the selection of drug-resistant mutants. If these data indicate acceptable hepatic safety, and taking into account potential pharmacokinetic interactions, studies in which an anti-HBV drug is combined with ART are encouraged.

Since the design of studies on co-infected patients with HBV and HIV may become complex, regulatory advice is recommended. In addition, the level of demonstration that could be considered acceptable to support a restricted indication in HIV-coinfected patients should be discussed with EU regulators. Whenever applicable, note should be taken to the NfG on medicinal products for treatment of HIV infection (CHMP/EWP/633/02 Rev. 1).

5.4 Co-Infected Patients with Hbv and Hepatitis C

Patients with co-infection with hepatitis C and hepatitis B need to assessed by quantitative PCR assays, for which virus that seems to predominate. Treatment studies must be designed accordingly. Clear criteria for the level of HBV DNA and HCV RNA that determine respective dominant disease and eligibility of the patients should be predefined in the study protocol. Under any circumstances viral loads of both HBV and HCV should be monitored during therapy and after cessation of treatment to assess efficacy and safety. In case combination treatment with interferon and ribavirin for hepatitis C, the level of HBV DNA when to add-on an anti-HBV agent should be pre-defined in the protocol.

6. CLINICAL SAFETY EVALUATION

Identified adverse events should be characterised in relation to duration of treatment, the dosage, the recovery time, age and other relevant factors. As for all medicinal products, tables should also summarise adverse events according to relevant patient characteristics, such as general condition at baseline (e.g. age, sex, hepato-renal function) and severity of infection, and according to at least the commonest concomitant medications.

Special attention should be given to withdrawal effects after drug discontinuation, in particular the risk of development of symptomatic/asymptomatic hepatitis flares and hepatic decompensation which should be carefully evaluated for several months after discontinuation of hepatitis B therapy.

The evaluation of safety in decompensated and liver transplant patients will be difficult due to the serious underlying disease process and the large number of concomitant medications. Thus, both the characterisation of the safety profile of a novel anti-HBV agent and especially the categorisation of events according to drug-relatedness are very difficult. The provision of safety data from comparative trials is preferred. Every effort must be made to provide narratives of patients who were withdrawn from therapy due to adverse events and for those that experienced serious adverse events and/or died regardless of causality. The tabulations should include rates of events in patients who were taking certain concomitant medications, whether or not there is any known likelihood of clinically significant interactions.

In combination trials, the combination should be compared to two drugs alone during the clinical development programme, since an increased risk of toxicity must be excluded.

6.1 Specific Adverse Events to be monitored

6.1.1 Adverse event depending of mechanism of action

Assessment of the potential adverse events according to the mechanism of action should be performed using a systematic and planned methodology. Any adverse events that might be predicted by the pre-clinical findings and any drug class-associated events, such as mitochondrial dysfunction, should be sought and followed with special care. Targeted monitoring and sometimes special studies are advisable for certain types of adverse events that are anticipated on this basis from chemical and/or pharmacological similarities between the antiviral product under evaluation and licensed medicinal products. Potential differences related to sex or ethnicity should always be explored.

6.1.2 Resistance development

The emergence of mutants with acquired resistance should be addressed as a safety issue. An evaluation of the potential for an anti-HBV agent to select for drug-resistant variants is an important part of the surveillance during therapy and after study completion. In addition, the outcome of patients with resistant strains and potential deterioration of liver disease need to be monitored during continued therapy and require long-term follow-up.

Data on resistance development and late post-treatment relapses is an important part of the long-term follow-up and should be regularly reported in the PSURs. Data should be presented separately as a specific issue to be clearly identified. As a part of the surveillance the potential for transmission of drug-resistant strains should be investigated.

6.1.3 Necessity to study next-line therapies

Depending on rate of resistance development and the possible severity of the consequences of treatment failure, the issues of salvage therapy and next-line therapy, however, might also have to be clarified before approval (see section 5.4.5)

6.2 Extent of Population Exposure to Assess Clinical Safety

The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A) applies.

6.3 Long term safety

The long-term safety of anti HBV therapy is important considering long-term maintenance therapy. Close monitoring of decompensated, liver transplant and HIV patients is important. Data on a large and representative group of patients for a sufficient period of time are needed.