Adverse Event (Pediatric)

General Instructions

If a patient experiences an unusual side effect or adverse event complete the Adverse Event (AE) form.

An Adverse Event form does not have to be completed for expected symptoms/signs of the underlying disease or common side effects of the study medication that are captured in the "Adverse Effects" section of the Visit Evaluation form.

Adverse Event Guidelines:

At a minimum, the following criteria should be used as a guide for recording events on the Adverse Event form. These guidelines are not all inclusive and the recording of events remains at the discretion of the investigator. A symptom or condition that is present but does not reach one of these levels may still be recorded as an adverse event.

1) A symptom or event that requires discontinuation of study medication.
2) A newly diagnosed symptom or event that requires a written prescription for treatment.
3) A newly diagnosed symptom or event that results in a referral to another provider.
4) Any grade 3 or 4 event according to the NCI Common Toxicity Criteria.

An adverse event is considered a **serious adverse event** if one or more of the following apply:

1. results in inpatient hospitalization or prolongs existing hospitalization
2. event is life-threatening
3. results in death
4. results in significant or permanent disability
5. requires medical intervention to prevent permanent damage
6. results in a congenital anomaly or birth defect

If an adverse event meets the criteria for a serious adverse event, complete both the Adverse Event form and the MedWatch form. Both forms should be completed and submitted to the DCC within 24 hours of knowledge of the event.

Each adverse event should have a date of onset and an outcome date, regardless of the duration of the event. Do not record the same event on more than one line if the event is continuing from one protocol evaluation to the next. Leave the Outcome Date and Outcome Status fields blank until the event either resolves or is determined to be continuing but controlled. If the Outcome Status is determined to be Continuing/controlled and then the patient has an exacerbation of that same event, record the new onset on a new line. Only new onsets should be recorded on a new line. If an adverse event evolves into a serious adverse event, follow the instructions in this MOP under "Outcome Status".

Specific Instructions

Patient ID**:** Record the Patient ID in the top right hand corner.

A System ID will be generated by the data entry system when you enter a record. Record that System ID on the data form if the adverse event information is being captured on paper.

Date of onset: Record the date (day/month/year) that the patient adverse event started. If any part of the date is unknown, record "Unk" [-3] in that field and complete the remaining fields.

Event type:	Record the code that indicates the event type and provide a brief description of the event in the Specify field. Refer to the current code list found on the project website.
Severity:	Using the following study definitions, (1) Record the code that indicates the initial severity of the episode. (2) Record the code that indicates the "most severe" severity of the episode. 1 = mild - easily tolerated condition or symptom 2 = moderate - discomfort that interferes with usual activity 3 = severe - incapacitating or causes inability to work or undertake usual activity 4 = life threatening
Serious adverse event:	Circle "Y" (yes) or "N" (no) to indicate if the adverse event meets the criteria of a serious adverse event. If yes, complete a MedWatch form and submit both the AE form and the MedWatch form to the DCC within 24 hours of knowledge of the event.
Unexpected:	Circle "Y" (yes) or "N" (no) to indicate if the adverse event is considered to be unexpected, in the opinion of the physician investigator. An event is considered to be unexpected if it is not mentioned in the investigational drug brochure or packet insert and it is not considered to be related to the natural history or progression of HBV disease.
Related to study drug:	Record the code that indicates the relationship of the event to each of the study medications, in the opinion of the physician investigator. 1 = unrelated (there is no reasonable causal relationship between the study drug and the AE) 2 = possibly related 3 = probably related 4 = definitely related
Drug dosing:	Record the code that indicates the effect of the event on each study drug dose. 1 = none 2 = reduced - drug dosage reduced due to adverse event 3 = interrupted - drug treatment interrupted due to adverse event 4 = discontinued - drug withdrawn due to adverse event
Outcome date:	Record the date (day/month/year) of the outcome of the adverse event. If the adverse event is continuing but not controlled this column should be left blank until the event is resolved or continuing and controlled. Some events may continue through the end of the study period before being resolved or determined to be continuing but controlled.
Outcome status:	For each adverse event, record the code that indicates the outcome status of the event. If the adverse event is continuing but not controlled record as Continuing. When the event is either Resolved or Controlled, update both the Outcome Date and Outcome Status on the form and in the database. If the adverse event evolves into a SAE, close out the adverse event by recording complete information for the AE until the time that it was determined to be a SAE. Record 'evolved into SAE' as the Outcome Status, and record the date that the AE was determined to be an SAE as the Outcome Date. Complete a new line for the SAE. The date of onset is the date that the AE was determined to be a SAE. Record all other information on that line pertaining to the SAE. 1 = Resolved - patient returned to previous health status with no subsequent problems

2 = Continuing - patient has not yet returned to previous health status and continues to be followed for the AE

3 = Controlled/stable - event is present but is controlled/stable.

4 = Evolved into SAE – an AE that evolves into a serious adverse event.

Events that are coded as Continuing will be reviewed periodically throughout the course of the study to determine whether they have Resolved or are Controlled.

System ID: Record the system generated ID for the record.

Adverse Events Requiring Expedited Reporting

An adverse event will be subject to expedited reporting if it meets all of the following criteria, according to the study-specific definitions below:

1) Serious in nature;
2) Related to the medicinal product;
3) Unexpected.

Serious Adverse Events

An adverse event will be considered to be **serious** if it results in any of the following:

- Death;
- Life-threatening;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Significant or permanent disability;
- Congenital anomaly/birth defect (in the case of an unanticipated birth to a study participant or to the female partner of a male study participant);
- Medical intervention to prevent permanent damage (e.g., intensive emergency treatment of allergic bronchospasm; blood dyscrasias or convulsions not requiring inpatient hospitalization; development of drug dependency or drug abuse).

Note that “serious” is used here to describe the outcome or action associated with an adverse event that could threaten a patient’s life or functioning. Thus, “serious” is distinguishable from “severe”, the latter referring to the degree or intensity of the specific event (e.g., mild, moderate, or severe).

Related to Medicinal Product

The phrase “**related to the medicinal product**” implies causality or attributability to the medicinal product. There currently exists no standard nomenclature to describe the degree of causality or attributability. An adverse event should be considered to be related to the medicinal product in situations in which a causal relationship cannot be ruled out. As noted above, the clinical center Physician Investigators will assess the degree of relatedness of the study medications and adverse events (i.e., unrelated, possibly related, probably related, definitely related).

Unexpected

The term **unexpected** refers to an adverse event that has not been previously observed or documented. In clinical studies, a guideline is needed to define an adverse event as either expected or unexpected based on previous observation. It is inappropriate to characterize the expectedness of an event based on extrapolation or anticipation from pharmacological properties of a medicinal product. The following documents or circumstances will be used to determine the expectedness of an adverse event:

- The Drug Labels which contain the clinical and non-clinical data on therapy with the study drugs.
- The natural history of chronic hepatitis B.
- Reports, which add significant information on specificity or severity of an otherwise known and documented adverse event, associated with the use of study drugs. Thus more severe or more specific adverse events than had previously been observed are considered unexpected.

To reiterate, an adverse event that is serious, related to the medicinal product, and unexpected is subject to expedited reporting. Expedited reporting is *not* required for events that are serious, but expected; nor is expedited reporting required for events that are non-serious, but expected. Expedited reporting is required, however, in situations in which there is an increased rate of occurrence of expected, serious adverse events related to the medicinal product (even marginally).

Sufficient data on adverse events requiring expedited reporting will be obtained to enable clinical center personnel to complete the MedWatch form, which will then be submitted to the appropriate safety oversight persons or groups, through the Data Coordinating Center (DCC). The holder of the IND at the NIDDK will also be notified in the case of an adverse event requiring expedited reporting. These individuals will review the report, and may decide to convene the DSMB to discuss issues related to monitoring such events. The DSMB, as an advisory body to the NIH, may advise early termination of the trial for safety reasons or make other recommendations regarding modifications to the protocol.

In accordance with IND safety reporting regulations, the holder of the IND, assisted by the DCC, will provide reports of adverse events requiring expedited reporting to the appropriate drug review division of the FDA and all participating investigators in writing within the required time frame (15 calendar days of notification for written reports). Reports of serious, unexpected adverse events to the FDA will initially be conducted by telephone or fax within the required time frame (7 calendar days of notification by the clinical centers for telephone and fax safety reports). Following telephone/fax notification, written reports will be sent to the FDA.

The clinical centers are to report relevant adverse events to the DCC, within 24 hours of knowledge of the event so that notification can be provided as soon as possible following discovery of the event for reasons of patient safety. The clinical center physician investigators will be responsible for obtaining all information required to complete the adverse event report.

Adverse events will also be reported to the University of Pittsburgh IRB in accordance with their guidelines. The clinical center physician investigators will be responsible for reporting adverse events to their respective institution's IRB.

The DCC statistician, with oversight from the Safety Officers, will be responsible for ongoing monitoring of incidence rates of adverse events.

The DCC will include all adverse event information in the annual IND report to the FDA. The initial annual report will be within 60 days of the anniversary date that the IND went into effect. In addition, the DCC will provide the clinical centers with updated information on adverse events that occur throughout the study. This information may be used to change the protocol or consent form if necessary. The clinical centers will also need to provide this information to their respective IRB offices annually with their renewals, or in the timeframes required by their IRBs.

The FDA annual report will be prepared by the DCC project coordinator and statistician under the guidance of the Safety Officer with input from the clinical center investigators, as necessary. The DCC project coordinator will be responsible for obtaining required information from the pharmaceutical companies associated with the study drug.

KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF ADVERSE EVENTS

Patient Details:
- Study number
- Gender
- Age and/or date of birth
- Height and weight

Suspected Medicinal Product(s):
- Brand Name
- International Non-Proprietary Name
- Batch Number
- Indication (s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify units)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

Other Treatment(s):
- Concomitant medications (prescription and non-prescription) and non-medicinal therapies. Include same information as for suspected medicinal product

Details of Suspected Serious Adverse Event(s):
- Full description of reactions(s) including body site and severity as well as criteria for regarding this report as serious. In addition to description of signs and symptoms, a specific diagnosis for the event should be made if possible.
- Start date and time of onset of adverse event
- Stop date and time or duration of adverse event
- Dechallenge and rechallenge information
- Setting where event occurred (i.e. hospital, clinic, home)
- Outcome:
  - Information on recovery and sequelae
  - Tests and treatments required and results
  - Cause of death (if applicable) and possible relationship to suspected Serious Adverse Events
  - Post-mortem findings (if applicable)
  - Other relevant information to facilitate assessment of the case such as medical history including allergies, drug or alcohol abuse, family history, findings from special investigations.

Details on Reporter of Adverse Event (suspected Serious Adverse Event):
- Name
- Address
- Telephone Number
- Profession (specialty)

Administrative and Sponsor/Company Details:
- Source of report (i.e. clinical investigation report, literature, new animal study findings)
- Date adverse event report received by sponsor/manufacturer
- Location where event occurred
- Type of report filed: initial or follow-up
- Name and address of sponsor/manufacturer/company
- Name, address, telephone and FAX number of contact person in reporting company or institution
- Identifying regulatory code or number (i.e. IND or NDA number)
- Sponsor/manufacturer's identification number for the case (This is for tracking purposes for the initial and follow-up reports.)