Section 6. Study Product Considerations for Non- Pharmacy Staff

6. Introduction

This section provides information and instructions for non-pharmacy staff (i.e., clinic staff) related to randomization, transport, receiving the MTN-033 gel from pharmacy (dispensation of gel from pharmacy staff to clinic staff), and delivery of the study gel to study participants (provision of gel from clinic staff to study participant). Associated instructions for pharmacy staff are provided in the MTN-033 Pharmacy Study Product Management Procedures Manual, which will be made available to the MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to Section 10 (Counseling Considerations) of this SSP manual for product use instructions and guidance on study product adherence counseling.

6.1 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme. Study randomization will occur via the Medidata web-based system, as described in Section 12 (Data Collection) of this manual. After clinic staff have randomized a participant into the study (through completion of the Randomization CRF), designated pharmacy staff will have on-line, restricted access (via Medidata) to the Pharmacy Dispensation CRF completed at Visit 3 and Visit 5 that will confirm to the site pharmacist which study product sequence the participant has been randomized/enrolled into at Enrollment. This field will be auto populated on the Pharmacy Dispensation CRF by Medidata Balance once the form is saved. From that information, the pharmacist will confirm how many gel applicators (1 or 4) to dispense for a given participant at a given visit (Visit 3 or 5). Clinic staff will complete a study prescription based on study product information indicated on the completed Randomization CRF and send the original part to designated site pharmacy staff, as described in section 6.2 below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed study gel.

Sixteen participants will receive dapivirine gel 0.05%, 2.5 g (applicator-only phase) and up to 10 g (coital simulation device phase). The sequence of the method of administration will be randomized to a single dose of dapivirine gel administered via an applicator followed by a single dose of the gel administered via a coital simulation device (Sequence A) or the reverse sequence of methods (Sequence B). There will be a two- to four-week washout period between the methods of administration.

	N	Period 1 (Visit 3)	Washout ~2-4 weeks	Period 2 (Visit 5)
Sequence A	8	One dapivirine gel applicator (2.5 g) administered into rectum		Up to 10 g administered into rectum via coital simulation device
Sequence B	8	Up to 10 g administered into rectum via coital simulation device		One dapivirine gel applicator (2.5 g) administered into rectum

6.2 Prescription Completion and Dispensing Study Gel at Visit 3 and Visit 5

The sequence of the gel administration method will be randomized to a single dose of dapivirine gel rectally administered via an applicator followed by gel administered via a coital simulation device (Sequence A) or the reverse sequence of administration methods (Sequence B).

Prescriptions (Appendix 6-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the prescriptions and for contacting the MTN LOC Pharmacist should additional prescriptions be needed during the study.

The CRS Name and ID are printed on the prescription. After recording the PTID and other details on the prescription, clinic staff will separate the two sheets of the form, and the white original will be delivered to the pharmacy. The yellow copy (bottom) will be retained in the participant's study notebook in the clinic. One prescription will be used for each participant for the dispensation of a single dose of gel (2.5 g; 1 applicator) and for the dispensation of 4 applicators of gel (10 grams) for use with the coital simulation device. Therefore, two prescriptions will be used for each participant; one at Visit 3 and one at Visit 5.

A prescription must be signed by an authorized prescriber as designated on FDA Form 1572. Corrections to the study prescriptions should only be made by study staff authorized to complete the original prescription. The same corrections should be made separately on both the original white sheet and the yellow copy. A signed and dated note explaining the corrections, if necessary, should also be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

Study gel will be dispensed directly to study staff on behalf of the participant, upon receipt of an original, written study prescription that is signed by an authorized prescriber. The pharmacist will dispense:

- Sequence A: One (1) gel applicator at Visit 3 and four (4) gel applicators at Visit 5.
- Sequence B: Four (4) gel applicators at Visit 3 and one (1) gel applicator at Visit 5.

In Clinic (procedures C1-C5):

C1. At Visit 2 (Enrollment Visit), the Inclusion/Exclusion Criteria CRF and Randomization CRF must be completed by clinic staff for a participant to be enrolled/randomized into the study. A participant is considered officially enrolled after the completion of the Randomization CRF, as evidenced by the appearance of a randomization date and time on the CRF.

C2. At Visit 3 and Visit 5, clinic staff will complete an MTN-033 Prescription (Appendix 6-1) accordingly. The participant's assigned study product sequence will be indicated on the Randomization CRF. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form prior to recording his/her initials.

C3. All sections of the prescription must be completed. A study staff member designated on the site's delegation of duties (DoA) log as an authorized prescriber of study product must print, sign, and date the bottom of the prescription. This person must also be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

C4. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook.

C5. Deliver the white (pharmacy) original prescription to the study pharmacy.

In Pharmacy (procedures P1-P3):

P1. At Visit 2, designated site pharmacy staff will receive a Medidata email alert confirming that the participant was enrolled/randomized into the study. This communication will be printed and filed in the pharmacy binder.

P2. Upon receiving the completed MTN-033 Prescription (at Visit 3 and Visit 5), the pharmacist will review the document for completion and accuracy by comparing it to the Study Product Sequence auto-populated on the Pharmacy Dispensation CRF in the Medidata study database for the given PTID. Note: Auto population of the study product sequence to which the participant was randomized will not be visible until the CRF is saved by the pharmacist. If pharmacy staff identifies possible errors on the prescription, s/he will return the prescription to clinic staff for clarification or correction. If corrections are required, they must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections should also be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes.

P2. Pharmacy staff will dispense the study product for participants per instructions in the MTN-033 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

6.3 Study Gel Request Slip

The MTN-033 Study Gel Request Slip (Appendix 6-2) is used by clinic staff to communicate to the study pharmacist the following actions:

- Additional product is needed/resupply (one or more of the applicators dispensed at Visit 3 or Visit 5 with the Prescription becomes unusable)
- Temporary product hold
- Study product resume after a temporary hold
- Permanent study product discontinuation
- Participant decline of study product use
- Product use period completed

The request slip will be produced as two-part no carbon required (NCR) sheets. The top white form is the original (pharmacy), and the bottom yellow form is the copy (clinic). Bulk supplies of the slips are available from the MTN LOC Pharmacist and will be supplied to clinic staff. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional request slips be needed during the study. The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. Clinic staff comments may also be provided if needed.

Double-check the accuracy of all entries and then separate the two parts of the completed slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections should also be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.3.1 Resupply of Study Product

During Visit 3 and Visit 5, RESUPPLY of study gel may be necessary due to, but not limited to, the following reasons:

- Damaged gel applicator(s) or packaging. Such occurrences must be reported to the site PoR as study product complaints, in addition to the request for more study product.
- Gel applicators dropped on floor or someplace dirty.
- Gel inappropriately dispensed from applicator.

6.3.2 Temporary Hold and Resume of Study Product

If a study clinician determines that a participant should temporarily hold study product use due to safety reason(s) (e.g., an adverse event), mark the “HOLD” box on the MTN-033 Study Gel Request Slip. Record the reason for the hold on the adjacent “Reason” line. It is not necessary to complete any new slips at subsequent visits in which the hold is still in effect. Once a product hold is in effect, the site pharmacist will not dispense any study product to that participant until the pharmacist receives a new request slip from the site clinic marked “RESUME”. Only clinic staff members who are authorized prescribers may mark the “RESUME” box. In all other circumstances, the slips are not required to be signed by an authorized prescriber, however site-specific pharmacy regulations may be more stringent. The study site must comply with local requirements. The “RESUME” box should only be checked if study product is being requested and dispensed following a product hold.

6.3.3 Participant-Initiated Decline of Study Product

If a participant decides on his/her own to stop using study gel, and refuses to be re-supplied further study product, mark the "PARTICIPANT DECLINE" box on the MTN-033 Study Gel Management Slip. Complete the slip and mark "PARTICIPANT DECLINE" at each subsequent visit that the participant refuses study product. If the participant declines product use, the PSRT should be notified.

6.3.4 Permanent Discontinuation of Study Product

If a study clinician determines that a participant should permanently discontinue study product use due to safety reason(s) (e.g., HIV infection), mark the "PERMANENT DISCONTINUATION" box. Record the reason for the permanent discontinuation on the "Reason" line provided. Once a permanent discontinuation is in effect, the site pharmacist will not dispense any further study product to that participant. Future slips will no longer be completed at the participant's remaining study visits. A Product Discontinuation CRF must also be completed by clinic staff.

6.3.5 Scheduled and Early Terminations

When a participant has completed his/her study participation, whether in the context of a scheduled or early termination visit, mark the "PRODUCT USE PERIOD COMPLETED" box on the MTN-033 Study Gel Management Slip. This serves as a notification to the site pharmacist that the participant no longer requires any additional study product dispensations. A Product Discontinuation and Study Discontinuation CRF should also be completed by clinic staff.

6.3.6 Study Gel Chain of Custody

Study gel will be dispensed from the pharmacy to an authorized clinic staff member who will then deliver the applicator(s) to the clinic for either insertion by the participant (1 applicator only) or for use with a coital simulation device (4 applicators). The site must designate its Chain of Custody (dispensing method) for study product in MTN-033 standard operating procedures (SOPs) for product dispensing and re-supply during MTN-033. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

6.3.7 Dispensing from the Pharmacy to Clinic Staff

To dispense study product to clinic staff, Prescriptions and Request Slips are expected to be delivered to the pharmacy by clinic staff. Upon receipt of a correctly completed and signed prescription or study product request slip, the PoR will prepare the requested quantity of study gel applicators as documented on the prescription or slip.

The MTN-033 Record of Receipt of Site-Specific Study Gel must be used to document dispensing of study product to clinic staff (chain of custody of study product from pharmacy staff to non-pharmacy staff). For the Record of Receipt, pharmacy staff will complete the top section (CRS name, CRS ID) and the first four columns in the body of the record. When receiving study product from the pharmacy for a given participant, clinic staff will verify and record the PTID in the designated column, confirm the quantity of study product dispensed, as documented by the site pharmacist, and complete the remaining two columns in the body of the record. Comments may be

recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the site pharmacy.

Clinic staff is responsible for controlling access to the study products dispensed into their custody and ensuring that the products are delivered to the participants for whom they were dispensed. Clinic staff must also document delivery of the study products to the designated participants in the participants' study charts. Delivery may be documented in chart notes or on other source documents used for this purpose. If all study products dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the study products to the pharmacy as soon as the participant's visit is completed or as soon as it is known that the participant will not be completing his/her study visit on the scheduled date.

6.4 Study Gel Use Instructions – Rectal Administration

Participants will either rectally insert one (1) gel applicator full of dapivirine 0.05% gel at Visit 3 and use up to approximately ten (10) grams of dapivirine 0.05% gel with a coital simulation device at Visit 5 or the reverse dosing sequence. The clinic staff will maintain a supply of the study provided lubricant (5 mL packets), which will be provided by the MTN LOC pharmacist. One packet should be provided to each participant for the single gel applicator dose.

Detailed instructions pertaining to both single gel applicator dose and the use of gel with a coital simulation device for both clinic staff and participants are found on the MTN-033 Study Implementation webpage. A list of frequently asked questions pertaining to rectal administration of a single applicator full of gel is available in Appendix 6-3.

6.5 Prohibited Medications

Certain medications are prohibited during study participation. These include anticoagulants, aspirin (greater than 81 mg/day), NSAIDS, other drugs that can increase bleeding risk, rectally administered medications or products that contain N-9 or corticosteroids, specified CYP3A4 inhibitors and inducers, and hormone-replacement therapy in tablet, injectable, patch, or gel form. Additionally, pre-exposure prophylaxis (PrEP) and post exposure prophylaxis (PEP) regimens are not permitted during trial participation. Medications listed in Protocol Section 9.3 warrant permanent discontinuation of study gel. The PSRT must be consulted if a participant uses other prohibited medication(s). Please refer to Protocol Sections 5.3, 6.8.1 and 9.3 and SSP Section 7 (Clinical Considerations) for details.

6.5.1 CYP3A4 Inhibitors and Inducers

Dapivirine is a CYP3A4 substrate – it is metabolized by CYP3A4. Study staff must promote the avoidance of CYP3A4 inhibitors and inducers (prescription medications, over-the-counter medications, herbal supplements, and nutritional supplements) via oral, injectable, vaginal or rectal route of administration. Appendix 6-4 outlines CYP3A4 inhibitors that participants should avoid using concomitantly in this study. Appendix 6-5 outlines CYP3A4 inducers to be avoided.

Information in Appendices 6-4 and 6-5 is adapted from:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4

If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-033 PSRT (mtn033psrt@mtnstopshiv.org). Medications with unknown interactions will be dealt with on a case-by-case basis with input from the PSRT, as needed.

6.5.2 Other Prohibited Medications

Study staff will counsel participants to avoid the use of medications that can increase bleeding risk – these include anticoagulants, blood modifier agents, and non-steroidal anti-inflammatory drugs (NSAIDS). Refer to Appendix 6-6 for a list of anticoagulants/blood modifier agents for participants to avoid. Refer to Appendix 6-7 for a list of prohibited NSAIDS. Additionally, the use of hormone therapy, including hormone replacement therapy, PrEP, PEP, perianally applied topical steroids, and rectally-administered medications, including products containing N-9, are also prohibited.

Other prohibited medications and practices can be found in Protocol Section 6.8.1 and SSP Section 7 (Clinical Considerations). If questions about prohibited medications arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-033 PSRT (mtn033psrt@mtnstopshiv.org). Inquiries will be dealt with on a case-by- case basis with input from the PSRT, as needed.

6.5.3 Study Gel Complaints

During the study, a problem or concern may be observed with a gel applicator. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may pertain to the dosage form (gel), packaging (overwrap pouch, cap, barrel, plunger), or other aspects of the study product. Clinic staff should make thorough record of complaints by participants and clinic staff. The clinic staff member will notify (via email) the site PoR and other designated site pharmacy staff of the study product complaint. This notification should include as much detail as possible and pictures (if necessary). The following information should be provided in the email:

- PTID
- date of the observed issue
- date that the issue was reported
- date gel was dispensed from pharmacy
- whether an adverse event occurred
- description of the nature of the issue, and any other details deemed necessary.

The site PoR will forward (via email) this information to the MTN LOC Pharmacist. If the complaint/issue concerns an unused gel applicator, then the unused gel applicator should be quarantined in the pharmacy. If the complaint/issue concerns a used gel applicator, then the clinic staff should document this in a communication to the pharmacy and /or provide a photo describing the issue (if available) and dispose of the applicator per clinic SOP(s).

Appendix 6-1: The MTN-033 Study Gel Prescription

MTN-033 PRESCRIPTION

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction. Once prescription is completed, deliver white original to pharmacy. File yellow copy in the participant's study notebook.

CRS Name and ID:	University of Pittsburgh CRS 1001

Participant ID: ☐☐☐ – ☐☐☐☐☐☐

Did the participant provide written informed consent for enrollment into MTN-033?	Yes ☐	No ☐	Clinic Staff Initials: _____

Dapivirine 0.05% Gel

Indicate Sequence:

	Period 1 (Visit 3)	Period 2 (Visit 5)
☐ A	2.5 g of dapivirine gel administered into rectum (One (1) applicator)	Up to 10 g of dapivirine gel administered into rectum via coital simulation device (Four (4) applicators)
☐ B	Up to 10 g of dapivirine gel administered into rectum via coital simulation device (Four (4) applicators)	2.5 g of dapivirine gel administered into rectum (One (1) applicator)

Indicate Study Period:

☐ Period 1 (Visit 3) ☐ Period 2 (Visit 5)

Check appropriate box for product to be dispensed:

☐ One (1) dapivirine gel applicator	☐ Four (4) dapivirine gel applicators
Sig: Insert entire contents of one (1) pre-filled applicator into the rectum. **Quantity:** One (1) pre-filled 0.05% dapivirine gel 2.5 g applicator. May be refilled as needed per request by designated clinic staff on MTN-033 Study Gel Request Slip for duration of participation in the study.	**Sig:** Apply the contents of up to four (4) pre-filled applicators to a coital simulation device for administration. **Quantity:** Four (4) pre-filled 0.05% dapivirine gel 2.5 g applicators. May be refilled as needed per request by designated clinic staff on MTN-033 Study Gel Request Slip for duration of participation in the study.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Appendix 6-2: The MTN-033 Study Gel Request

MTN-033 STUDY GEL REQUEST SLIP

Clinic Staff Instructions: Once slip is completed, deliver white original (labeled "Pharmacy") to the pharmacy. File yellow copy (labeled "Clinic") in the participant's study notebook.

Participant ID: ☐☐☐ – ☐☐☐☐☐☐ **Visit #:** _____

☐ **RE-SUPPLY** → **Pharmacy:** Dispense _____ dapivirine gel applicator(s).

Reason: _____

☐ **HOLD** → **Reason:** _____

Pharmacy: **Do not** dispense further applicators to the participant until another MTN-033 Study Gel Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy:** Dispense _____ dapivirine gel applicator(s).

Requires authorized prescriber signature.

☐ **PARTICIPANT DECLINE** → **Pharmacy:** **Do not** dispense at this visit, participant is choosing not to use product.

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____

Pharmacy: **Do not** dispense any further applicators to the participant.

☐ **PRODUCT USE PERIOD COMPLETED** → **Pharmacy:** **Do not** dispense any further applicators to the participant.

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Appendix 6-3: Rectal Gel Use Frequently Asked Questions – Single Gel Applicator Dose

1. What is the best position to insert the gel rectally?
   A. Find the position that feels the most comfortable to you. Many people may already have a position that they prefer. If you do not have a preferred position, we recommend that you stand or lie on your side to insert the gel rectally.

2. What should I do if it hurts when I use the applicator to insert the gel?
   A. Before rectal gel application, make sure there is lubricant on the outside of the applicator, as inserting a dry applicator may cause discomfort. You should also not force the applicator into the rectum.

3. Where does the gel go to after I put it inside?
   A. The study gel stays in the rectum. It is unlikely that any of the gel will leak from the rectum. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the rectum. If this happens you should contact the study staff.

4. Can the applicator get lost inside me?
   A. No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body. Once the contents are inserted, remove the entire applicator and discard.

5. What should I do if I have trouble applying the gel with the applicator?
   A. The applicators should be easy to use rectally. The applicator, when used rectally, should be slightly lubricated with the lubricant provided by the clinic staff. If you have difficulty using the applicators, ask study staff for help, as they may be able to show you different ways that you can insert the gel, which might make it easier.

6. What should I do if I think there is something wrong with an applicator?
   A. If there seems to be something wrong with an applicator (for example, you find it difficult to push the study gel out of the applicator, or if study gel has leaked out, or you think there is some other problem), do not use the applicator. Immediately alert clinic staff.

7. What happens if I press the plunger too early and most of the gel comes out on my outside? Can I put more in?
   A. If most of the study gel comes out on your outside, let study staff know and they will provide you with a new applicator to use.

8. What happens if the applicator gets wet before I need to use it?
   A. If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open. Ask clinic staff for guidance.

9. What should I do if the wrapper is already open when I want to use the gel?
   A. You should only use an applicator with a sealed wrapper, so you should always open the wrapper right before inserting the gel. If you receive an applicator with an unsealed wrapper, do not use the applicator and alert study staff.

10. What should I do if I forget to come to the clinic and use the gel?
    A. If you miss an appointment, call the clinic staff immediately. If you are unable to come to the clinic the same day as your missed appointment, you may be able to reschedule your appointment for a later date within your visit window.

11. What should I do if I have a reaction to the study gel at home (e.g., unusual itching, stinging)?
    A. Contact the study staff and ask their advice. They might ask you to go to the clinic to be assessed and receive treatment, if needed.

12. Can I use the study gel before sex?
    A. Participants must abstain from inserting any non-study products into the rectum for 72 hours prior to and following clinic visits. Participants should also abstain from the following for 72 hours before and after biopsy collection and PK sample collection: receptive anal intercourse (RAI), receptive oral anal stimulation (i.e., rimming), rectal stimulation via fingers, as well as the insertion of any non-study products into the rectum.

Appendix 6-4: CYP3A4 Inhibitors to Avoid

Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	**Moderate Inhibitors ≥2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak Inhibitors* ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
Antibiotics: clarithromycin, telithromycin Antidepressants: nefazodone Azole Antifungals: ketoconazole, itraconazole, posaconazole, voriconazole Pharmacokinetic Enhancers: cobicistat Protease Inhibitors: ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, boceprevir, telaprevir Reverse Transcriptase Inhibitors: delavirdine Vasopression Receptor Antagonists: conivaptan	Antiarrhythmics: dronedarone Antibiotics: erythromycin, ciprofloxacin Antiemetics: aprepitant Antineoplastics: imatinib Azole Antifungals: fluconazole, miconazole Calcium Channel Blockers: verapamil, diltiazem Protease Inhibitors: atazanavir, darunavir/ritonavir, fosamprenavir	Antiandrogens: bicalutamide Antianginals: ranolazine Antiarrhythmics: amiodarone, quinidine Antibiotics: azithromycin Antidepressants: fluoxetine, fluvoxamine Antihyperlipidemics: atorvastatin Anti-inflammatory (asthma): zileuton Antineoplastics: nilotinib Antituberculars: isoniazid Anxiolytics: alprazolam Calcium Channel Blockers: amlodipine, felodipine Herbal Supplements: ginkgo biloba, goldenseal Histamine H2 Antagonists: cimetidine, ranitidine Immune Suppressants: cyclosporine Platelet Aggregation Inhibitors: cilostazol Protease Inhibitors: tipranavir/ritonavir

Appendix 6-5: CYP3A4 Inducers to Avoid

Strong Inducers **≥ 80% decrease in AUC**	**Moderate Inducers** **50-80% decrease in AUC**	**Weak Inducers*** **20-50% decrease in AUC**
Anticonvulsants/Mood Stabilizers: phenytoin, carbamazepine Anticonvulsants/Barbiturates: primidone Antituberculars: rifampin Barbiturates: phenobarbital, butalbital Glucocorticoids: dexamethasone Herbal Supplements: St. John's wort^ Protease Inhibitors: tipranavir (alone)	Antibiotics: nafcillin Antihypertensives: bosentan Antituberculars: rifabutin CNS Stimulants: modafinil Reverse Transcriptase Inhibitors: efavirenz, etravirine, nevirapine	Anticonvulsants: oxcarbazepine, rufinamide Antidiabetics: pioglitazone CNS Stimulants: armodafinil Glucocorticoids: prednisone Herbal Supplements: echinacea^ Protease Inhibitors: amprenavir

*Mild inducers/inhibitors are permitted as long as a stable dose is anticipated throughout the study.

^The effect of St. John's wort and echinacea varies widely and is preparation-dependent.

AUC: Area under the curve in a plot of concentration of drug in blood/systemic circulation versus time. AUC (from zero to infinity) represents the total drug exposure over time.
CL: ClearanceAppendix 6-6: Anticoagulants/Blood Modifier Agents to Avoid

Apixaban (Eliquis) Clopidogrel sulfate (Plavix) Dabigatran (Pradaxa) Dalteparin (Fragmin) Enoxaparin sodium (Lovenox) Fondaparinux (Arixtra) Heparin
Prasugrel (Effient)
Rivaroxaban (Xarelto)
Ticagrelor (Brillinta)
Warfarin (Coumadin)

Appendix 6-7: NSAIDS to Avoid

Aspirin (greater than 81mg/day; Anacin, Ascriptin, Bayer, Bufferin, Ecotrin, Excedrin*)
Choline and magnesium salicylates (CMT, Tricosal, Trilisate)
Choline salicylate (Anthropan)
Celecoxib (Celebrex)
Diclofenac potassium (Cataflam)
Diclofenac sodium (Voltaren, Voltaren XR)
Diflunisal (Dolobid)
Etodolac (Lodine, Lodine XL)
Fenoprofen calcium (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Advil, Motrin,Nuprin)
Indomethacin (Indocin, Indocin SR)
Ketoprofen (Actron, Orudis, Oruvail)
Ketorolac (Toradol)
Magnesium salicylate (Arthritab, Bayer Select, Magan, Mobidin, Mobogesic)
Meclofenamate sodium (Meclomen)
Mefenamic acid (Ponstel)
Meloxicam (Mobic)
Nabumetone (Relafen)
Naproxen, naproxen sodium (Naprosyn, Naprelan, Aleve, Anaprox)
Oxaprozin (Daypro)
Piroxicam (Feldene)
Rofecoxib (Vioxx)
Salsalate (Amigesic, Anaflex 750, Disalcid, Marthritic, Mono-Gesic, Salflex, Salsitab)
Sodium salicylate (various)
Sulindac (Clinoril)
Tolmetin sodium (Tolectin)
Valdecoxib (Bextra)
***Note: some products, such as Excedrin, are combination products. Excedrin contains aspirin, acetaminophen, and caffeine. Aspirin free Excedrin is available.**