Significance Rating

1 2 3 4 5

A number 1 through 5 will be assigned to each interaction monograph, based on the Editorial Group's assessment of the interaction's Severity and Documentation (defined below).

1 is a severe and well-documented interaction.

5 is an interaction of no more than unlikely or possible documentation.

The formula for these number ratings is given in the following table:

Significance Rating	Severity	Documentation
1	Major	Suspected or >
2	Moderate	Suspected or >
3	Minor	Suspected or >
4	Major/Moderate	Possible
5	Minor	Possible
	Any	Unlikely

Onset

How rapidly the clinical effects of an interaction can occur determines the urgency with which preventive measures should be instituted to avoid the consequences of the interaction. Two levels of onset are used:

Rapid: The effect will be evident within 24 hours of administration of the interacting drug. *Immediate action is necessary to avoid the effects of the interaction.*

Delayed: The effect will not be evident until the interacting drug is administered for a period of days or weeks. *Immediate action is not required.*

Severity

The potential severity of the interaction is particularly important in assessing the risk vs benefit of therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule, the negative effects of most interactions can be avoided. Three degrees of severity are defined:

Major: The effects are potentially life-threatening or capable of causing permanent damage.

Moderate: The effects may cause a deterioration in a patient's clinical status. Additional treatment, hospitalization, or an extended hospital stay may be necessary.

Minor: The effects are usually mild; consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome. Additional treatment is usually not required.

Documentation

Documentation determines the degree of confidence that an interaction can cause an altered clinical response. This scale represents the Editorial Group's evaluation of the quality and clinical relevance of the primary literature supporting the occurrence of an interaction. However, multiple factors can influence whether

even a well-documented interaction occurs in a particular patient. The documentation does not address the incidence or frequency of the interaction; it is also independent of the potential severity of the effect of the interaction.

The following guidelines are used to establish the five Documentation levels:

Established: Proven to occur in well-controlled studies.

- An altered pharmacologic effect *has been demonstrated in well-controlled human studies* ... or ...
- A pharmacokinetic interaction *has been demonstrated in well-controlled human studies.* An altered pharmacologic response is expected based on the magnitude of the kinetic effect; clinical observations support the occurrence of the interaction.

Probable: Very likely but not proven clinically.

- A pharmacokinetic interaction has been demonstrated in well-controlled studies. Based on the magnitude of the kinetic changes and the known plasma level-response relationship of the affected drug, an altered pharmacologic response will *probably* occur ... or ...
- When controlled human experimentation is impractical, well-designed animal experiments confirm an interaction that is suggested by multiple case reports or uncontrolled studies.

Suspected: May occur; some good data; needs more study.

- A pharmacokinetic interaction has been demonstrated in well-controlled studies. Although an altered pharmacologic response *might be expected to occur* based on the magnitude of the kinetic changes, *no firm conclusion can be drawn* because a plasma level-response relationship has not been established for the affected drug ... or ...
- An altered pharmacologic response has been reported in multiple case reports or repeated uncontrolled clinical studies.

Possible: Could occur, but data are very limited.

- Although a pharmacokinetic interaction has been demonstrated, the kinetic changes are of such magnitude that it is *not possible to predict* if an altered response will occur ... or ...
- The evidence is divided as to whether an interaction exists ... or ...
- An altered pharmacologic response is suggested by limited data.

Unlikely: Doubtful; no good evidence of an altered clinical effect.

- A pharmacokinetic interaction has been demonstrated; however, based on the magnitude of kinetic change, a *pharmacologic alteration is unlikely* ... or ...
- *The bulk of documentation is of poor quality* or does not favor the existence of an interaction.
- In spite of reports of an interaction, well-controlled studies refute the existence of a clinically relevant interaction.

Drug interactions assigned Documentation levels of "Established," "Probable," or "Suspected" are considered to be reasonably well substantiated and have a significance rating of "1," "2," or "3." It is the opinion of the Editorial Group that these interactions have a reasonable probability of occurring.

Drug interactions assigned a Significance Rating of "4" or "5" have a Documentation level of "Possible" or "Unlikely" and are not substantiated. Because there is insufficient evidence supporting the existence of a clinically relevant interaction, prospective screening is probably not warranted. If an unanticipated effect occurs, the information in these monographs will be useful in reviewing what is known about these potential interactions.