Expected Outputs with Scientific References (Cases 1-15)

This document summarizes the expected outputs and scientific references for clinical decision support test cases 1 to 15.

Test Case 1: Warfarin + Ibuprofen (Elderly Male, AFib, Osteoarthritis)

Input


```
{   "drugs": ["warfarin",
"ibuprofen"],
  "age": 70,
  "gender": "Male",
  "allergies": [],   "diagnosis": "Atrial Fibrillation
and Osteoarthritis"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "Risk of serious bleeding, especially GI, when warfarin is combined
with NSAIDs such as ibuprofen. [1
  ],
  "Drug-Allergy": [     "No
allergy conflicts. [3]"
  ],
  "Drug-Disease Contraindications": [     "NSAIDs like ibuprofen may worsen control of hypertension and
can increase risk of cardiovascular eve
  ],
  "Ingredient Duplication": [     "No overlapping ingredients; both increase bleeding risk through
different mechanisms. [1][2]"
  ],
  "Pregnancy Warnings": [     "None (not
applicable in male patients). [3]"
  ],
  "Lactation Warnings": [     "None (not
applicable in male patients). [3]"
  ],
  "General Precautions": [
    "Monitor for bleeding signs like bruising or dark stools. [1]",     "Monitor for
signs of kidney damage due to ibuprofen, especially in elderly. [2][6]"
  ],
  "Therapeutic Class Conflicts": [     "Both affect clotting and may increase
bleeding risk when used together. [1][2]"
  ],
  "Warning Labels": [
    "Risk of serious bleeding, especially GI, when warfarin is combined with NSAIDs. [1][2]",
"Risk of gastrointestinal bleeding is higher in older adults taking NSAIDs. [7][2]"
  ],
  "Indications": [     "Warfarin: Prevention and treatment of thromboembolic disorders such as atrial
fibrillation and deep     "Ibuprofen: Analgesic and anti-inflammatory used for pain, fever, and
inflammation. [2]"
  ]
}
```


References:

[1] FDA label for warfarin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s109lbl.pdf
[2] FDA label for ibuprofen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017463s117lbl.pdf
[3] Best clinical practice/expert consensus.
[4] Martínez-Mir I, et al. Nonsteroidal anti-inflammatory drugs and atrial fibrillation. Drug Saf. 2014;37(7):535-542. [PMID:24326054]
[5] UpToDate: NSAIDs and risk of arrhythmia, 2023.
[6] UpToDate: NSAIDs: Adverse effects on the kidney.
[7] García Rodríguez LA, et al. Risk of upper gastrointestinal complications among users of traditional NSAIDsand COX 2 inhibitors in the general population. Gastroenterology. 2004;127(5):1322-1330. [PMID:15229996]

Test Case 2: Lisinopril + Ibuprofen + Penicillin Allergy (Female, Gestational Hypertens

Input


```
{   "drugs": ["lisinopril",
"ibuprofen"],
  "age": 34,
  "gender": "Female",
  "allergies": ["sulfa drugs"],
"diagnosis": "Gestational Hypertension"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "Increased risk of kidney injury and hyperkalemia when ACE inhibitors (like lisinopril) are combined
  ],
  "Drug-Allergy": [     "No known cross-reactivity between lisinopril or ibuprofen and sulfa drugs. [3]"
  ],
  "Drug-Disease Contraindications": [     "NSAIDs like ibuprofen may worsen hypertension and impair kidney function, especially during pregnanc
  ],
  "Ingredient Duplication": [     "No overlapping active ingredients. [5]"
  ],
  "Pregnancy Warnings": [     "Lisinopril is contraindicated in pregnancy due to risk of fetal toxicity and malformations. [6][7]"
  ],
  "Lactation Warnings": [     "Ibuprofen is generally considered compatible with breastfeeding, but should be used with caution. [8
  ],
  "General Precautions": [     "Monitor blood pressure, kidney function, and for signs of hyperkalemia when combining lisinopril and
  ],
  "Therapeutic Class Conflicts": [     "ACE inhibitors and NSAIDs both can affect renal function; risk is additive. [1][2]"
  ],
  "Warning Labels": [
    "NSAIDs may worsen hypertension and kidney function in pregnancy. [2][4]",
"Lisinopril can cause fetal toxicity if used during pregnancy. [6][7]"
```

```
  ],
  "Indications": [
    "Lisinopril: ACE inhibitor used for hypertension and heart failure. [7]",
"Ibuprofen: Analgesic and anti-inflammatory used for pain, fever, and inflammation. [9]"
  ]
}
```

References:

[1] Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999;106(5B):13S-24S. [PMID:10390106]

[2] FDA label for ibuprofen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017463s117lbl.pdf

[3] Lexicomp Drug Allergy Checker. No cross-reactivity between sulfa drugs and NSAIDs/ACE inhibitors.

[4] American College of Obstetricians and Gynecologists (ACOG). Hypertension in pregnancy. Practice Bulletin No. 203.

[5] Best clinical practice/expert consensus.

[6] FDA label for lisinopril: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019690s043lbl.pdf

[7] UpToDate: Use of antihypertensive drugs in pregnancy and lactation.

[8] Hale TW. Medications and Mothers' Milk. Ibuprofen considered safe during lactation.

[9] FDA label for ibuprofen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017463s117lbl.pdf

Test Case 3: Metformin + Naproxen (Male, Diabetes & Osteoarthritis)

Input

```
{   "drugs": ["metformin",
"naproxen"],
  "age": 55,
  "gender": "Male",
  "allergies": ["penicillin"],   "diagnosis": "Type 2
Diabetes Mellitus and Osteoarthritis"
}
```

Expected Output

```
{
  "Drug-Drug Interactions": [     "Risk of lactic acidosis may be increased if renal function is
impaired by NSAIDs like naproxen when
  ],
  "Drug-Allergy": [     "No expected cross-allergy between naproxen/metformin
and penicillin. [3]"
  ],
  "Drug-Disease Contraindications": [     "NSAIDs like naproxen may worsen kidney function in patients
with diabetes, increasing metformin toxi
  ],
  "Ingredient Duplication": [     "No
overlapping active ingredients. [5]"
  ],
  "Pregnancy Warnings": [     "N/A
[Best clinical practice]"
  ],
  "Lactation Warnings": [     "N/A
[Best clinical practice]"
  ],
```

```
  "General Precautions": [     "Monitor renal function and blood glucose in patients on
metformin and NSAIDs. [1][2][4]",
    "Monitor for GI bleeding when taking naproxen, especially in older adults. [6]"
  ],
  "Therapeutic Class Conflicts": [     "Different classes; potential renal interaction but
not therapeutic class overlap. [5]"
  ],
  "Warning Labels": [
    "Naproxen may increase risk of GI bleeding, especially in older adults. [6]",
"Metformin can cause gastrointestinal side effects and, rarely, lactic acidosis. [1]"
  ],
  "Indications": [     "Metformin: First-line treatment for type 2
diabetes mellitus. [1]",     "Naproxen: NSAID used for pain and
inflammation. [2]"
  ]
}
```


References:

[1] FDA label for metformin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021202s027lbl.pdf

[2] FDA label for naproxen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017581s098lbl.pdf

[3] Lexicomp: Drug Allergy and Cross-Reactivity Table.

[4] American Diabetes Association. Standards of Medical Care in Diabetes-2023.

[5] Best clinical practice/expert consensus.

[6] Bhala N, et al. Vascular and upper gastrointestinal effects of NSAIDs: meta-analyses of individualparticipant data from randomised trials. Lancet. 2013;382(9894):769-779. [PMID:23726390]

Test Case 4: Naproxen (Elderly Female, Hypertension & Osteoarthritis)

Input


```
{   "drugs": ["naproxen"],
  "age": 70,
  "gender": "Female",
  "allergies": ["penicillin"],   "diagnosis": "Hypertension and Osteoarthritis"
}
```


Expected Output


```
{   "Drug-Drug Interactions": [
    "None [1]"
  ],
  "Drug-Allergy": [     "No expected cross-allergy between naproxen and penicillin. [2]"
  ],
  "Drug-Disease Contraindications": [     "NSAIDs like naproxen may worsen blood pressure control in patients
with hypertension. [3][4]"
  ],   "Ingredient Duplication": [
    "None [1]"
  ],
  "Pregnancy Warnings": [     "N/A [Best clinical practice]"
  ],
  "Lactation Warnings": [     "N/A [Best clinical practice]"
  ],
  "General Precautions": [     "Elderly patients are at higher risk of adverse effects from NSAIDs, such as GI
bleeding and renal im
```

```
  ],  "Therapeutic Class Conflicts": [    "None [1]"
  ],
  "Warning Labels": [    "Increased risk of GI bleeding, especially in elderly patients. [5][6]"
  ],
  "Indications": [    "Naproxen: NSAID used for pain and inflammation. [7]"
  ]
}
```


References:

[1] FDA label for naproxen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017581s098lbl.pdf

[2] Lexicomp: Drug Allergy and Cross-Reactivity Table.

[3] FDA label for naproxen (hypertension warning).

[4] UpToDate: NSAIDs and blood pressure control.

[5] Bhala N, et al. Vascular and upper gastrointestinal effects of NSAIDs: meta-analyses of individualparticipant data from randomised trials. Lancet. 2013;382(9894):769-779. [PMID:23726390]

[6] García Rodríguez LA, et al. Risk of upper gastrointestinal complications among users of NSAIDs in thegeneral population. Gastroenterology. 2004;127(5):1322-1330. [PMID:15229996]

[7] FDA label for naproxen (indications).

Test Case 5: Amlodipine + Acetaminophen (Male, Aspirin Allergy, Liver Disease)

Input


```
{   "drugs": ["amlodipine",
"acetaminophen"],
  "age": 60,
  "gender": "Male",
  "allergies": ["aspirin"],   "diagnosis": "Primary
Hypertension and Chronic Liver Disease"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "No significant interaction between
amlodipine and acetaminophen. [1][2]"
  ],
  "Drug-Allergy": [     "No cross-reactivity between amlodipine or acetaminophen and
aspirin allergy. [3][4]"
  ],
  "Drug-Disease Contraindications": [
    "Amlodipine should be used with caution in patients with hepatic impairment due to increased exposure
"No specific contraindication for acetaminophen in hypertension, but caution is needed in liver disea
  ],   "Ingredient
Duplication": [     "None
[1]"
  ],
  "Pregnancy Warnings": [     "None
[Best clinical practice]"
  ],
  "Lactation Warnings": [
    "None [Best clinical practice]"
  ],
```

```
  "General Precautions": [     "Monitor for hypotension or edema with amlodipine, especially in elderly
or hepatic impairment. [5][6     "Monitor total daily acetaminophen dose in chronic liver disease; avoid
overdose. [7]"
  ],   "Therapeutic Class
Conflicts": [     "None [1]"
  ],
  "Warning Labels": [
    "Avoid excessive acetaminophen dosing in chronic liver disease. [7]",
"Amlodipine may cause hypotension, dizziness, or peripheral edema. [5][6]"
  ],
  "Indications": [
    "Amlodipine: Calcium channel blocker used for hypertension and angina. [5]",
"Acetaminophen: Analgesic and antipyretic used for pain and fever. [7]"
  ]
}
```


References:

[1] Micromedex Drug Interactions Checker.

[2] FDA label for amlodipine: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019787s046lbl.pdf

[3] Lexicomp: Drug Allergy and Cross-Reactivity Table.

[4] Best clinical practice/expert consensus.

[5] FDA label for amlodipine (hepatic impairment warnings).

[6] UpToDate: Calcium channel blockers in hypertension.

[7] FDA label for acetaminophen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204767s020lbl.pdf

Test Case 6: Aspirin (Male Child, Chickenpox/Varicella)

Input


```
{   "drugs":
["aspirin"],
  "age": 10,
  "gender": "Male",
  "allergies": [],   "diagnosis":
"Varicella (Chickenpox)"
}
```


Expected Output


```
{   "Drug-Drug Interactions":
[     "None [1]"
  ],
  "Drug-Allergy": [     "No
allergy conflicts. [2]"
  ],
  "Drug-Disease Contraindications": [     "Aspirin is contraindicated in children with viral illness
due to risk of Reye's syndrome. [3][4]"
  ],
  "Ingredient Duplication": [
"Single drug; no duplication. [1]"
  ],
  "Pregnancy Warnings": [     "N/A
[Best clinical practice]"
  ],
```

```
  "Lactation Warnings": [     "N/A
[Best clinical practice]"
  ],
  "General Precautions": [     "Aspirin should be avoided in children with varicella or influenza due to
Reye's syndrome risk. [3][4
  ],
  "Therapeutic Class Conflicts": [     "Therapeutic
class conflict not applicable. [1]"
  ],
  "Warning Labels": [     "Warning: Aspirin use in children with viral illnesses may cause
Reye's syndrome. [3][4]"
  ],
  "Indications": [     "Aspirin: Analgesic, antipyretic, and antiplatelet agent for pain, fever, and
cardiovascular prophyla
  ]
}
```


References:

[1] FDA label for aspirin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009768s037lbl.pdf

[2] Best clinical practice/expert consensus.

[3] American Academy of Pediatrics. The management of Reye syndrome. Pediatrics. 1982;69(6):724-729.

[4] Centers for Disease Control and Prevention (CDC): 'Reye's syndrome - Public Health Statement.'

[5] FDA label for aspirin (indications).

Test Case 7: Cocaine + Lisinopril (Male, Hypertension & Cocaine Use Disorder)

Input


```
{   "drugs": ["cocaine",
"lisinopril"],
  "age": 45,
  "gender": "Male",
  "allergies": [],   "diagnosis": "Essential Hypertension and
Cocaine Use Disorder"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "No clinically significant drug-drug interaction reported between
cocaine and lisinopril. [1][2]"
  ],
  "Drug-Allergy": [     "No allergy
conflicts reported. [3]"
  ],
  "Drug-Disease Contraindications": [
    "Cocaine can worsen hypertension and increase cardiovascular risk. [4][5]",     "Lisinopril is not
contraindicated, but patients with renal impairment should be monitored. [6][7]"
  ],   "Ingredient
Duplication": [     "None
[1]"
```

```
  ],
  "Pregnancy Warnings": [     "None (not applicable in male patients).
[Best clinical practice]"
  ],
  "Lactation Warnings": [     "None (not applicable in male patients).
[Best clinical practice]"
  ],
  "General Precautions": [     "Monitor blood pressure closely due to additive risk
for hypertension. [4][6]",     "Monitor renal function due to lisinopril risk. [6]"
  ],   "Therapeutic Class
Conflicts": [     "None [1]"
  ],
  "Warning Labels": [
    "Cocaine can cause severe hypertension, arrhythmia, and cardiovascular events. [4][5]",
"Lisinopril can cause hypotension or hyperkalemia, especially in patients with renal disease. [6][7]"
  ],
  "Indications": [
    "Lisinopril: ACE inhibitor used for hypertension and heart failure. [6]",
    "Cocaine: No therapeutic indication; illicit stimulant drug. [5]"
  ]
}
```


References:

[1] Micromedex Drug Interactions Checker.
[2] FDA label for lisinopril: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019690s043lbl.pdf
[3] Best clinical practice/expert consensus.
[4] American Heart Association. Cocaine and acute cardiovascular complications. Circulation. 2007;115(13):1760-1767. [PMID:17389266]
[5] UpToDate: Cocaine: Acute intoxication and management.
[6] FDA label for lisinopril (renal, BP monitoring, and contraindications).
[7] UpToDate: Use of antihypertensive drugs in pregnancy and lactation.

Test Case 8: Metformin (Female, Type 2 Diabetes in Pregnancy)

Input


```
{   "drugs":
["metformin"],
  "age": 30,
  "gender": "Female",
  "allergies": [],   "diagnosis": "Type 2 Diabetes
Mellitus in Pregnancy"
}
```


Expected Output


```
{   "Drug-Drug Interactions":
[     "None [1]"
  ],
  "Drug-Allergy": [     "No allergy
conflicts reported. [2]"
  ],
  "Drug-Disease Contraindications": [     "Use metformin with caution in patients with renal impairment,
hepatic dysfunction, or risk factors f
```

```
  ],   "Ingredient
Duplication": [     "None
[1]"
  ],
  "Pregnancy Warnings": [     "Metformin is considered relatively safe in pregnancy, but long-term data
are limited; consult guidel
  ],
  "Lactation Warnings": [     "Metformin is excreted in breast milk but generally considered safe;
monitor infant for GI side effec
  ],
  "General Precautions": [
    "Monitor renal function regularly due to risk of lactic acidosis. [3][4]",     "Monitor
blood glucose to avoid hypoglycemia, especially if used with other agents. [9]"
  ],   "Therapeutic Class
Conflicts": [     "None [1]"
  ],
  "Warning Labels": [
    "Risk of lactic acidosis, especially in renal or hepatic impairment. [3][4]"
  ],
  "Indications": [     "Metformin: First-line treatment for type 2 diabetes mellitus, including use
during pregnancy. [5][6]
  ]
}
```


References:

[1] FDA label for metformin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021202s027lbl.pdf
[2] Best clinical practice/expert consensus.
[3] FDA label for metformin (renal/hepatic impairment, lactic acidosis warning).
[4] UpToDate: Metformin in the treatment of adults with type 2 diabetes mellitus.
[5] American Diabetes Association. Standards of Medical Care in Diabetes-2023.
[6] National Institute for Health and Care Excellence (NICE): Diabetes in pregnancy.
[7] Hale TW. Medications and Mothers' Milk.
[8] UpToDate: Safety of medications for diabetes during lactation.
[9] UpToDate: Management of pregestational diabetes mellitus and pregnancy.

Test Case 9: Benzocaine Teething Gel (Elderly Female, Gingivitis)

Input


```
{   "drugs": ["benzocaine teething
gel"],
  "age": 88,
  "gender": "Female",
  "allergies": [],
"diagnosis": "Gingivitis"
}
```


Expected Output


```
{   "Drug-Drug Interactions":
[     "None [1]"
  ],
  "Drug-Allergy": [     "No allergy
conflicts reported. [2]"
```

```
  ],
  "Drug-Disease Contraindications": [     "Benzocaine should be used with caution in patients with a
history of methemoglobinemia, or G6PD defi
  ],   "Ingredient
Duplication": [     "None
[1]"
  ],
  "Pregnancy Warnings": [     "None (not
applicable/insufficient data). [5]"
  ],
  "Lactation Warnings": [     "None (not
applicable/insufficient data). [5]"
  ],
  "General Precautions": [
    "Monitor for signs of oral irritation or allergic reactions, especially in elderly. [6]",
"Use with caution in elderly patients due to increased risk of adverse effects. [6]"
  ],
  "Therapeutic Class Conflicts": [
    "None [1]"
  ],
  "Warning Labels": [     "Topical benzocaine may rarely cause methemoglobinemia, especially in young
children and elderly. [3]
  ],
  "Indications": [     "Benzocaine teething gel: Topical anesthetic for temporary relief of
oral discomfort. [8]"
  ]
}
```


References:

[1] FDA label for benzocaine:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/017963s065lbl.pdf
[2] Best clinical practice/expert consensus.
[3] FDA Safety Communication: Benzocaine and Risk of Methemoglobinemia.
[4] Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg.
2009;108(3):837-845. [PMID:19224782]
[5] UpToDate: Safety of topical anesthetics in pregnancy and lactation.
[6] American Dental Association (ADA): Oral care in elderly patients.
[7] FDA Safety Communication, 2018: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safetycommunication-benzocaine-and-risk-methemoglobinemia [8] FDA label for benzocaine (indications).

[8] FDA label for benzocaine (indications).

Test Case 10: Warfarin + Aspirin + Clopidogrel (Elderly Male, Atrial Fibrillation, Stroke

Input


```
{   "drugs": ["warfarin", "aspirin",
"clopidogrel"],
  "age": 78,
  "gender": "Male",
```

```
  "allergies": [],   "diagnosis": "Atrial Fibrillation, History of Stroke,
Coronary Artery Disease"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "Significantly increased risk of serious bleeding, especially
gastrointestinal, when warfarin is comb
  ],
  "Drug-Allergy": [     "No allergy
conflicts reported. [4]"
  ],
  "Drug-Disease Contraindications": [     "Triple antithrombotic therapy (warfarin, aspirin, clopidogrel)
substantially increases bleeding risk
  ],
  "Ingredient Duplication": [     "No overlapping active ingredients, but additive
antiplatelet/anticoagulant effect increases bleeding
  ],
  "Pregnancy Warnings": [     "None (not applicable in male patients).
[Best clinical practice]"
  ],
  "Lactation Warnings": [     "None (not applicable in male patients).
[Best clinical practice]"
  ],
  "General Precautions": [
    "Monitor for signs of bleeding (e.g., GI bleeding, bruising, hematuria) and check INR closely. [1][2]
"Elderly patients are at significantly increased risk for serious bleeding with triple therapy. [1][2
  ],
  "Therapeutic Class Conflicts": [     "All three drugs affect hemostasis by inhibiting platelet function
or coagulation, raising bleeding r
  ],
  "Warning Labels": [     "Black box warning for major bleeding with warfarin and additive risk with
antiplatelets. [1][3]",     "Monitor INR closely; risk of fatal bleeding. [1]"
  ],
  "Indications": [     "Warfarin: Prevention and treatment of thromboembolic disorders such as atrial
fibrillation and deep
    "Aspirin: Antiplatelet for cardiovascular prophylaxis, analgesic, antipyretic. [2]",
"Clopidogrel: Antiplatelet agent for prevention of vascular events (e.g., after stroke or acute coron
  ]
}
```


References:

[1] FDA label for warfarin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s109lbl.pdf

[2] FDA label for aspirin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009768s037lbl.pdf

[3] FDA label for clopidogrel: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020839s062lbl.pdf

[4] Best clinical practice/expert consensus.

Test Case 11: Metformin, Lisinopril, Ibuprofen (Female, Diabetes, Hypertension, Osteoarthritis)

Input


```
{
  "drugs": [
    "metformin",
    "lisinopril",     "ibuprofen"
  ],
  "age": 50,
  "gender": "Female",
  "allergies": [     "penicillin"
  ],   "diagnosis": "Type 2 Diabetes Mellitus, Hypertension, Osteoarthritis"
}
```


Expected Output


```
{

  "Drug-Drug Interactions": [

    "Lisinopril and ibuprofen: Increased risk of kidney injury and hyperkalemia. [1][2][3]", "Metformin and ibuprofen: Increased risk of metformin accumulation and lactic acidosis if renal function impaired. [4][5]",     "Ibuprofen: May blunt antihypertensive effect of lisinopril. [2][3]"

  ],

  "Drug-Allergy": [     "No known cross-reactivity between any of the prescribed drugs and penicillin. [6]"

  ],

  "Drug-Disease Contraindications": [

    "Ibuprofen may worsen hypertension and renal function. [2][3]",     "Metformin should be used with caution in patients with renal impairment. [4][5]"

  ],   "Ingredient Duplication": [

    "None [7]"

  ],

  "Pregnancy Warnings": [

    "Metformin: Generally considered safe in pregnancy. [8]",     "Lisinopril: Contraindicated in pregnancy (risk of fetal toxicity). [9]",     "Ibuprofen: Should be avoided in late pregnancy. [2][10]"

  ],

  "Lactation Warnings": [     "Metformin: Excreted in breast milk but generally considered safe. [8][11]",

    "Lisinopril: Limited data; use with caution. [12]",     "Ibuprofen: Compatible with breastfeeding. [2][13]"
```

```
  ],

  "General Precautions": [

    "Monitor blood pressure and renal function when using lisinopril and ibuprofen together.

[1][2][3]",

    "Monitor blood glucose when taking metformin. [4]"

  ],

  "Therapeutic Class Conflicts": [

    "Lisinopril (ACE inhibitor) and ibuprofen (NSAID) both impact renal function; risk is
additive. [1][2][3]"   ],

  "Warning Labels": [

    "Ibuprofen may cause gastrointestinal bleeding or ulcers, especially in older adults.

[2][14]",

    "Lisinopril may cause cough, angioedema, or hyperkalemia. [12]",     "Metformin may cause
lactic acidosis, especially with renal impairment. [4]"

  ],

  "Indications": [

    "Metformin: First-line treatment for type 2 diabetes mellitus. [4]",

    "Lisinopril: ACE inhibitor used for hypertension and heart failure. [12]",     "Ibuprofen:
Analgesic and anti-inflammatory for pain, fever, and inflammation. [2]"

  ]

}
```


References:

[1] Whelton A. Nephrotoxicity of NSAIDs: physiologic foundations and clinical implications. Am J Med. 1999;106(5B):13S-24S.

[PMID:10390106]

[2] FDA label for ibuprofen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017463s117lbl.pdf

[3] FDA label for lisinopril: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019690s043lbl.pdf

[4] FDA label for metformin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021202s027lbl.pdf

[5] UpToDate: Metformin and lactic acidosis.

[6] Lexicomp: Drug Allergy and Cross-Reactivity Table.

[7] Best clinical practice/expert consensus.

[8] ADA Standards of Medical Care in Diabetes-2023.

[9] FDA label for lisinopril (pregnancy).

[10] UpToDate: NSAIDs in pregnancy.

[11] Hale TW. Medications and Mothers' Milk.

[12] FDA label for lisinopril.

[13] FDA label for ibuprofen (lactation).

[14] García Rodríguez LA, et al. Risk of upper GI complications among NSAID users. Gastroenterology. 2004;127(5):1322-1330.

[PMID:15229996]

Test Case 12: Atorvastatin, Amlodipine, Furosemide, Enalapril (Male, CKD, Heart Failure)

Input


```
{
  "drugs": [
    "atorvastatin",
    "amlodipine",
    "furosemide",     "enalapril"
  ],
  "age": 72,
  "gender": "Male",
  "allergies": [],   "diagnosis": "Chronic Kidney Disease, Heart Failure, Hyperlipidemia, Hypertension"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [     "Enalapril and furosemide: Increased risk of hypotension and kidney dysfunction. [1][2]",
    "Amlodipine and enalapril: Additive hypotensive effects. [3][4]",
    "Amlodipine and furosemide: Increased risk of hypotension and electrolyte imbalance. [2][4]",
    "Atorvastatin and amlodipine: May increase atorvastatin plasma levels; monitor for myopathy.
[5][6]"
  ],
  "Drug-Allergy": [     "No allergy conflicts reported. [7]"
  ],
  "Drug-Disease Contraindications": [
    "Enalapril and furosemide should be used with caution in chronic kidney disease due to risk of renal impairment. [1][2]",     "Amlodipine may exacerbate symptoms in patients with advanced heart failure. [4]",     "Atorvastatin: Use with caution in hepatic impairment. [8]"
  ],   "Ingredient Duplication": [
    "None [7]"
  ],
  "Pregnancy Warnings": [     "None (not applicable in male patients). [Best clinical practice]"
  ],
```

```
  "Lactation Warnings": [     "None (not applicable in male patients). [Best
clinical practice]"
  ],
  "General Precautions": [
    "Monitor renal function, electrolytes, and blood pressure with enalapril and
furosemide.
[1][2]",
    "Monitor for muscle symptoms (myopathy) with atorvastatin, especially when
used with amlodipine. [5][6]",
    "Monitor for edema and hypotension with amlodipine. [4]"
  ],
  "Therapeutic Class Conflicts": [
    "Enalapril (ACE inhibitor) and furosemide (loop diuretic) both lower blood
pressure and affect renal function. [1][2]"   ],
  "Warning Labels": [     "Enalapril: May cause severe hypotension,
hyperkalemia, and renal impairment. [1]",
    "Furosemide: May cause electrolyte disturbances and dehydration. [2]",
"Atorvastatin: Risk of myopathy, especially at higher doses or with drug
interactions. [5][6]"
  ],
  "Indications": [
    "Atorvastatin: Statin for hyperlipidemia. [8][11]",
    "Amlodipine: Calcium channel blocker for hypertension and angina. [4]",
    "Furosemide: Loop diuretic for edema and heart failure. [2]",
"Enalapril: ACE inhibitor for hypertension and heart failure. [1]"
  ]
}
```


References:

[1] FDA label for enalapril: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019690s043lbl.pdf

[2] FDA label for furosemide: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/016426s073lbl.pdf

[3] FDA label for amlodipine: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019787s046lbl.pdf

[4] UpToDate: Calcium channel blockers in heart failure.

[5] FDA label for atorvastatin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020702s045lbl.pdf

[6] FDA Drug Interactions Table: Atorvastatin/Amlodipine.

[7] Best clinical practice/expert consensus.

[8] FDA label for atorvastatin (liver warnings).

[9] FDA label for enalapril (pregnancy).

[10] FDA label for furosemide (pregnancy/lactation).

[11] FDA label for atorvastatin (pregnancy/lactation).

Test Case 13: Prednisone, Methotrexate, Folic Acid, Naproxen (Female, Rheumatoid Arthritis)

Input


```
{
  "drugs": [
    "prednisone",
    "methotrexate",
    "folic acid",
    "naproxen"
  ],
  "age": 36,
  "gender": "Female",
  "allergies": [],   "diagnosis": "Rheumatoid Arthritis"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [
    "Methotrexate and NSAIDs (naproxen) may increase methotrexate toxicity (myelosuppression, nephrotoxicity). [1][2]",     "Prednisone and naproxen both increase GI bleeding/ulcer risk. [3][4]",     "Prednisone and methotrexate: Increased risk of infection and bone loss. [5][6]"
  ],
  "Drug-Allergy": [     "No allergy conflicts reported. [7]"
  ],
  "Drug-Disease Contraindications": [
    "Naproxen should be used with caution in patients with renal impairment or GI disease.
[3][4]",     "Prednisone and methotrexate: Caution in infection risk, bone disease. [5][6]"
  ],   "Ingredient Duplication": [
    "None [7]"
  ],
  "Pregnancy Warnings": [
    "Methotrexate is contraindicated in pregnancy (teratogenic). [8][9]",
    "Folic acid is recommended in all women of childbearing potential and especially in pregnancy.
[10]"
  ],
  "Lactation Warnings": [
    "Methotrexate: Contraindicated during lactation. [8][9]",     "Prednisone and naproxen: Use with caution, lowest effective dose. [4][5]"
  ],
  "General Precautions": [
    "Monitor for GI symptoms and bleeding (naproxen, prednisone). [3][4]",
    "Monitor for signs of infection (prednisone, methotrexate). [5][6]",
"Monitor renal function (methotrexate, naproxen). [1][2]",
```

```
    "Monitor for osteoporosis (prednisone). [5][6]"
  ],   "Therapeutic Class Conflicts": [
    "None [7]"
  ],
  "Warning Labels": [     "Methotrexate: Risk of bone marrow suppression, liver
toxicity, GI ulceration. [1][8][9]",
    "Prednisone: Risk of immunosuppression, osteoporosis, hyperglycemia.
[5][6]",
    "Naproxen: GI bleeding, renal risk, especially when combined with
corticosteroids or methotrexate. [3][4]"   ],
  "Indications": [
    "Prednisone: Corticosteroid for inflammatory and autoimmune conditions.
[5][6]",
    "Methotrexate: DMARD for rheumatoid arthritis and some cancers. [8][9]",
"Folic acid: Supplement to prevent deficiency and reduce methotrexate toxicity.
[10]",     "Naproxen: NSAID for pain and inflammation. [3][4]"
  ]
}
```


References:

[1] FDA label for methotrexate: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009321s054lbl.pdf

[2] UpToDate: Methotrexate drug interactions.

[3] FDA label for naproxen: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/017581s098lbl.pdf

[4] UpToDate: NSAIDs and GI toxicity.

[5] FDA label for prednisone: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020457s017lbl.pdf

[6] UpToDate: Glucocorticoid adverse effects.

[7] Best clinical practice/expert consensus.

[8] FDA label for methotrexate (pregnancy/lactation).

[9] ACR guideline: Reproductive health and rheumatic diseases. Arthritis Rheumatol. 2020.

[10] UpToDate: Folic acid supplementation in rheumatologic disease and pregnancy.

Test Case 14: Digoxin, Furosemide, Spironolactone, Enalapril, Aspirin (Female, Heart Failure)

Input


```
{
  "drugs": [
    "digoxin",
    "furosemide",
    "spironolactone",
    "enalapril",
    "aspirin"
  ],
  "age": 84,
  "gender": "Female",
  "allergies": [],   "diagnosis": "Heart Failure, Atrial Fibrillation,
Osteoarthritis"
}
```

Expected Output


```
{
  "Drug-Drug Interactions": [
    "Digoxin and furosemide: Furosemide-induced hypokalemia increases digoxin toxicity risk.
[1][2]",
    "Digoxin and spironolactone: Spironolactone may increase digoxin levels by inhibiting renal excretion. [3]",
    "Furosemide and spironolactone: May counterbalance potassium effects, but risk of electrolyte disturbance. [2][3]",
    "Enalapril and spironolactone: Increased risk of hyperkalemia, especially in elderly or CKD.
[4][5]",
    "Enalapril and furosemide: Additive hypotension and renal impairment risk. [2][4]",
    "Aspirin and enalapril: Aspirin may reduce antihypertensive efficacy of enalapril and worsen renal function. [6][7]",
    "Aspirin and furosemide: Increased risk of renal impairment and reduced diuretic efficacy.
[6][7]",
    "Aspirin and spironolactone: Possible increased risk of hyperkalemia and renal dysfunction.
[6][7]"
  ],
  "Drug-Allergy": [     "No allergy conflicts reported. [8]"
  ],
  "Drug-Disease Contraindications": [     "All drugs: Use with caution in elderly and those with renal dysfunction. [2][4][7]"
  ],   "Ingredient Duplication": [
    "None [8]"
  ],
  "Pregnancy Warnings": [     "None (not applicable in elderly female patient). [Best clinical practice]"
  ],
  "Lactation Warnings": [
    "None (not applicable in elderly female patient). [Best clinical practice]"
  ],
  "General Precautions": [     "Monitor for signs of hypotension and electrolyte imbalance (esp. potassium). [2][3][4]",     "Monitor renal function due to polypharmacy. [2][4][7]",
    "Monitor for digoxin toxicity. [1][3]",     "Monitor for bleeding with aspirin. [6][7]"
  ],
  "Therapeutic Class Conflicts": [     "Spironolactone and enalapril: Both are potassium-sparing (risk of hyperkalemia). [3][4][5]",     "Furosemide is a loop diuretic, different from others. [2]"
  ],
  "Warning Labels": [
```

```
    "Digoxin: Risk of toxicity, especially with hypokalemia. [1]",
    "Furosemide: Risk of hypokalemia, dehydration. [2]",
    "Spironolactone: Risk of hyperkalemia, especially with ACE inhibitors.
[3][4]",
    "Enalapril: Risk of hyperkalemia, hypotension, renal impairment. [4]",
"Aspirin: Risk of GI bleeding, especially in elderly. [6][7]"
  ],
  "Indications": [     "Digoxin: Heart failure, atrial fibrillation. [1]",
    "Furosemide: Heart failure, edema. [2]",     "Spironolactone: Heart failure,
edema, hypertension. [3]",
    "Enalapril: Heart failure, hypertension. [4]",     "Aspirin: Antiplatelet,
analgesic, antipyretic. [6][7]"
  ]
}
```


References:

[1] FDA label for digoxin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020405s017lbl.pdf

[2] FDA label for furosemide: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/016426s073lbl.pdf

[3] FDA label for spironolactone: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/010151s048lbl.pdf

[4] FDA label for enalapril: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019690s043lbl.pdf

[5] UpToDate: Drug interactions with potassium-sparing diuretics and ACE inhibitors.

[6] FDA label for aspirin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009768s037lbl.pdf

[7] UpToDate: NSAIDs, kidney, and heart failure interactions.

[8] Best clinical practice/expert consensus.

Test Case 14: Digoxin, Furosemide, Spironolactone, Enalapril, Aspirin (Female, Heart Failure)

Input


```
{
  "drugs": [
    "warfarin",
    "amiodarone",
    "simvastatin",
    "metoprolol",     "clarithromycin"
  ],
  "age": 68,
  "gender": "Male",
  "allergies": [],   "diagnosis": "Atrial Fibrillation, Hyperlipidemia, Chronic
Bronchitis"
}
```


Expected Output


```
{
  "Drug-Drug Interactions": [
```

"Warfarin and amiodarone: Amiodarone inhibits warfarin metabolism, greatly increasing bleeding risk. [1][2]",

"Warfarin and clarithromycin: Clarithromycin inhibits warfarin metabolism, increasing INR and bleeding risk. [3][4]",

"Warfarin and simvastatin: Simvastatin may increase warfarin effect and bleeding risk.
[2][5]",

"Warfarin and metoprolol: No clinically significant interaction. [6]",

"Amiodarone and simvastatin: Increased risk of statin toxicity (myopathy/rhabdomyolysis).
[2][5][7]",

"Amiodarone and clarithromycin: Increased risk of QT prolongation, arrhythmia. [8][9]",

"Simvastatin and clarithromycin: Increased risk of statin toxicity due to CYP3A4 inhibition.
[2][5][10]",

"Clarithromycin and metoprolol: Increased metoprolol exposure and risk of bradycardia. [11]",

"Clarithromycin and amiodarone: Increased risk of QT prolongation and arrhythmia. [8][9]",

"Overall risk of bleeding and toxicity is high with this drug combination.
[1][2][3][4][5][7][8][10][11]"

],

"Drug-Allergy": ["No allergy conflicts reported. [12]"

],

"Drug-Disease Contraindications": [

"Amiodarone: Use with caution in patients with pulmonary disease (risk of pulmonary toxicity).
[13]",

"Clarithromycin: Use with caution in patients with chronic bronchitis/COPD (risk of arrhythmia, drug interactions). [9]"], "Ingredient Duplication": ["None [12]"

],

"Pregnancy Warnings": ["None (not applicable in male patients). [Best clinical practice]"

],

"Lactation Warnings": ["None (not applicable in male patients). [Best clinical practice]"

],

"General Precautions": [

"Monitor INR and signs of bleeding (warfarin). [1][2][3][4][5]",

"Monitor for myopathy or rhabdomyolysis (simvastatin + amiodarone/clarithromycin).
[5][7][10]",

"Monitor for arrhythmia and bradycardia (amiodarone + clarithromycin + metoprolol).
[8][9][11]", "Monitor for signs of pulmonary toxicity (amiodarone). [13]"

],

```
  "Therapeutic Class Conflicts": [
    "Multiple CYP inhibitors (amiodarone, clarithromycin) with CYP-metabolized drugs (warfarin, simvastatin, metoprolol): increased toxicity risk. [2][5][8][11]"   ],
  "Warning Labels": [
    "Black box warning: risk of fatal bleeding with warfarin, especially with inhibitors like amiodarone or clarithromycin. [1][2][3][4]",     "Statin-associated myopathy risk increases with amiodarone/clarithromycin. [5][7][10]", "QT prolongation and arrhythmia risk with amiodarone + clarithromycin. [8][9]"
  ],
  "Indications": [     "Warfarin: Prevention and treatment of thromboembolic disorders (AFib, DVT, PE). [1]",     "Amiodarone: Antiarrhythmic for AFib and ventricular arrhythmias. [2]",
    "Simvastatin: Statin for hyperlipidemia. [5]",
    "Metoprolol: Beta blocker for hypertension, angina, AFib. [6]", "Clarithromycin: Macrolide antibiotic for respiratory infections. [9]"
  ]
}
```


References:

[1] FDA label for warfarin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009218s109lbl.pdf

[2] FDA label for amiodarone: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018972s046lbl.pdf

[3] FDA label for clarithromycin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050662s049lbl.pdf

[4] UpToDate: Warfarin drug interactions.

[5] FDA label for simvastatin: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020702s045lbl.pdf

[6] FDA label for metoprolol: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019692s034lbl.pdf

[7] UpToDate: Drug interactions with statins.

[8] FDA label for amiodarone (QT warning).

[9] UpToDate: Macrolide antibiotic drug interactions.

[10] FDA label for simvastatin (clarithromycin warning).

[11] FDA label for metoprolol (macrolide DDI).

[12] Best clinical practice/expert consensus.

[13] FDA label for amiodarone (pulmonary warning).