Atlantic Biologicals Corps
RISPERIDONE -risperidone solution Atlantic Biologicals Corps
----------HIGHLIGHTS OFPRESCRIBING INFORMATION
These highlights donotinclude alltheinformation needed touseRisperidone safely andeffectively. seefullprescribing information forRisperidone. Risperidone (Risperidone) SOLUTION forORALuse.Initial U.S.Approval: 1993WARNING: INCREASED MORTALITY INELDERLY PATIENTS WITHDEMENTIA-RELATED
PSYCHOSIS See fullprescribing information forcomplete boxed warning Elderly patients withdementia-related psychosis treated withantipsychotic drugs areatanincreased risk
of death. Risperidone isnotapproved forthetreatment ofpatients withdementia-related
psychosis.[SeeWarnings andPrecautions (5.1)]INDICATIONS ANDUSAGE
Risperidone oralsolution, USPisanatypical antipsychotic agent indicated for:(1)Treatment ofschizophrenia inadults andadolescents aged13to17years (1.1)Alone, orincombination withlithium orvalproate, fortheshort-term treatment ofacute manic ormixed episodesassociated withBipolar IDisorder inadults, andalone inchildren andadolescents aged10to17years (1.2)Treatment ofirritability associated withautistic disorder inchildren andadolescents aged5to16years (1.3)DOSAGE ANDADMINISTRATION
Initial DoseTitrationTarget DoseEffective DoseRangeSchizophrenia- adults (2.1)2 mg/day1 to2mgdaily4 to8mgdaily4 to16mg/daySchizophrenia –adolescents
(2.1)0.5 mg/day0.5 to1mgdaily3 mg/day1 to6mg/dayBipolar mania –adults (2.2)2 to3mg/day1 mgdaily1 to6mg/day1 to6mg/dayBipolar mania inchildren/adolescents (2.2)0.5 mg/day0.5 to1mgdaily2.5 mg/day0.5 to6mg/day
Irritability associated with
autistic disorder (2.3)0.25 mg/day(<20 kg)0.5 mg
/day(≥20 kg)0.25 to0.5mgat≥
2weeks0.5 mg/day(<20 kg)1mg
/day(≥20 kg)0.5 to3mg/dayDOSAGE FORMS ANDSTRENGTHSOral solution: 1mg/mL (3)CONTRAINDICATIONSKnown hypersensitivity totheproduct (4)WARNINGS ANDPRECAUTIONSCerebrovascular events, including stroke, inelderly patients withdementia-related psychosis. Risperidone isnotapproved foruseinpatients withdementia-related psychosis (5.2)Neuroleptic Malignant Syndrome (5.3)Tardive dyskinesia (5.4)Hyperglycemia anddiabetes mellitus (5.5)Hyperprolactinemia (5.6)Orthostatic hypotension (5.7)Leukopenia, Neutropenia, andAgranulocytosis: hasbeenreported withantipsychotics, including risperidone. Patientswith ahistory ofaclinically significant lowwhite blood cellcount (WBC) oradrug-induced leukopenia/neutropenia
should havetheir complete blood count (CBC) monitored frequently during thefirst fewmonths oftherapy and
discontinuation ofrisperidone should beconsidered atthefirst signofaclinically significant decline inWBCinthe
absence ofother causative factors. (5.8)Potential forcognitive andmotor impairment (5.9)Seizures (5.10)Dysphagia (5.11)Priapism (5.12)Thrombotic Thrombocytopenic Purpura (TTP) (5.13)Disruption ofbodytemperature regulation (5.14)Antiemetic Effect (5.15)Suicide (5.16)
Increased sensitivity inpatients withParkinson’s disease orthose withdementia withLewybodies (5.17)Diseases orconditions thatcould affect metabolism orhemodynamic responses (5.17)ADVERSE REACTIONSThe mostcommon adverse reactions inclinical trials (≥10%) weresomnolence, increased appetite, fatigue, insomnia,sedation, parkinsonism, akathisia, vomiting, cough, constipation, nasopharyngitis, drooling, rhinorrhea, drymouth,abdominal painupper, dizziness, nausea, anxiety, headache, nasal congestion, rhinitis, tremor, andrash. (6)(6)The mostcommon adverse reactions thatwereassociated withdiscontinuation fromclinical trials werenausea,somnolence, sedation, vomiting, dizziness, andakathisia. (6)To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at1-877-835-5472 andorFDA at1-800-FDA-1088 orwww.amneal.comwww.fda.gov/medwatch. (6)DRUG INTERACTIONSDue toCNSeffects, usecaution whenadministering withother centrally-acting drugs. Avoid alcohol. (7.1)Due tohypotensive effects, hypotensive effects ofother drugs withthispotential maybeenhanced. (7.2)Effects oflevodopa anddopamine agonists maybeantagonized. (7.3)Cimetidine andranitidine increase thebioavailability ofrisperidone. (7.5)Clozapine maydecrease clearance ofrisperidone. (7.6)Fluoxetine andparoxetine increase plasma concentrations ofrisperidone. (7.10)Carbamazepine andother enzyme inducers decrease plasma concentrations ofrisperidone. (7.11)USE INSPECIFIC POPULATIONSNursing Mothers: should notbreast feed. (8.3)Pediatric Use:safety andeffectiveness notestablished forschizophrenia lessthan13years ofage,forbipolar mania
less than10years ofage,andforautistic disorder lessthan5years ofage.(8.4)Elderly ordebilitated; severe renal orhepatic impairment; predisposition tohypotension orforwhomhypotension
poses arisk: Lower initial dose(0.5mgtwice daily), followed byincreases indoseinincrements ofnomorethan0.5mg
twice daily. Increases todosages above 1.5mgtwice daily should occur atintervals ofatleast 1week. (8.5, 2.4)See 17forPATIENT COUNSELING INFORMATION.Revised: 12/2010FULL PRESCRIBING INFORMATION: CONTENTS*WARNING: INCREASED MORTALITY INELDERLY PATIENTS WITHDEMENTIA-RELATED PSYCHOSIS
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DEMENTIA-RELATED PSYCHOSISElderly patients withdementia-related psychosis treated withantipsychotic drugs areatan
increased riskofdeath. Analyses of17placebo-controlled trials (modal duration of10weeks), largely inpatients taking atypical antipsychotic drugs, revealed ariskofdeath in
drug-treated patients ofbetween 1.6to1.7times theriskofdeath inplacebo-treated
patients. Overthecourse ofatypical 10-week controlled trial, therateofdeath indrug-treated patients wasabout 4.5%, compared toarateofabout 2.6%intheplacebo group.Although thecauses ofdeath werevaried, mostofthedeaths appeared tobeeither
cardiovascular (e.g., heart failure, sudden death) orinfectious (e.g., pneumonia) innature.Observational studies suggest that, similar toatypical antipsychotic drugs, treatment with
conventional antipsychotic drugs mayincrease mortality. Theextent towhich thefindingsof increased mortality inobservational studies maybeattributed totheantipsychotic drug
as opposed tosomecharacteristic(s) ofthepatients isnotclear. Risperidone isnotapproved forthetreatment ofpatients withdementia-related psychosis.[SeeWarnings andPrecautions (5.1)]1 INDICATIONS &USAGE
1.1 SchizophreniaAdultsRisperidone oralsolution, USPisindicated fortheacute andmaintenance treatment ofschizophrenia .[seeClinical Studies (14.1)]AdolescentsRisperidone oralsolution, USPisindicated forthetreatment ofschizophrenia inadolescents aged13to
17 years .[seeClinical Studies (14.1)]1.2 Bipolar ManiaMonotherapy -Adults andPediatricsRisperidone oralsolution, USPisindicated fortheshort-term treatment ofacute manic ormixed
episodes associated withBipolar IDisorder inadults andinchildren andadolescents aged10to17
years .[seeClinical Studies (14.2)]Combination Therapy –AdultsThe combination ofrisperidone oralsolution, USPwithlithium orvalproate isindicated fortheshort-term treatment ofacute manic ormixed episodes associated withBipolar IDisorder [seeClinical Studies
(14.3)].1.3 Irritability Associated withAutistic DisorderPediatricsRisperidone oralsolution, USPisindicated forthetreatment ofirritability associated withautisticdisorder inchildren andadolescents aged5to16years, including symptoms ofaggression towardsothers, deliberate self-injuriousness, temper tantrums, andquickly changing moods .[seeClinical Studies
(14.4)]2 DOSAGE ANDADMINISTRATION
2.1 SchizophreniaAdultsUsual Initial DoseRisperidone oralsolution, USPcanbeadministered onceortwice daily. Initial dosing isgenerally 2mg/day. Doseincreases should thenoccur atintervals notlessthan24hours, inincrements of1to2mg/day, astolerated, toarecommended doseof4to8mg/day. Insomepatients, slower titration maybe
appropriate. Efficacy hasbeendemonstrated inarange of4to16mg/day .However, doses above 6mg/day fortwice daily dosing werenotdemonstrated tobemoreefficacious thanlower doses, were
associated withmoreextrapyramidal symptoms andother adverse effects, andaregenerally notrecommended. Inasingle study supporting once-daily dosing, theefficacy results weregenerally
stronger for8mgthanfor4mg.Thesafety ofdoses above 16mg/day hasnotbeenevaluated inclinical
trials. [seeClinical Studies (14.1)]Maintenance TherapyWhile itisunknown howlongapatient withschizophrenia should remain onrisperidone oralsolution,USP, theeffectiveness ofrisperidone oralsolution, USP2mg/day to8mg/day atdelaying relapse wasdemonstrated inacontrolled trial inpatients whohadbeenclinically stable foratleast 4weeks andwere
then followed foraperiod of1to2years .Patients should beperiodically reassessed todetermine theneed formaintenance treatment withanappropriate dose. [seeClinical Studies (14.1)]AdolescentsThe dosage ofrisperidone oralsolution, USPshould beinitiated at0.5mgoncedaily, administered asa
single-daily doseineither themorning orevening. Dosage adjustments, ifindicated, should occur at
intervals notlessthan24hours, inincrements of0.5or1mg/day, astolerated, toarecommended doseof 3mg/day. Although efficacy hasbeendemonstrated instudies ofadolescent patients with
schizophrenia atdoses between 1and6mg/day, noadditional benefit wasseenabove 3mg/day, and
higher doses wereassociated withmoreadverse events. Doses higher than6mg/day havenotbeen
studied.Patients experiencing persistent somnolence maybenefit fromadministering halfthedaily dosetwicedaily.There arenocontrolled datatosupport thelonger termuseofrisperidone oralsolution, USPbeyond 8weeks inadolescents withschizophrenia. Thephysician whoelects touserisperidone oralsolution,USP forextended periods inadolescents withschizophrenia should periodically re-evaluate thelong-term risks andbenefits ofthedrugfortheindividual patient.Reinitiation ofTreatment inPatients Previously DiscontinuedAlthough there arenodatatospecifically address reinitiation oftreatment, itisrecommended thatafteran interval offrisperidone oralsolution, USP,theinitial titration schedule should befollowed.Switching FromOther AntipsychoticsThere arenosystematically collected datatospecifically address switching schizophrenic patients
from other antipsychotics torisperidone oralsolution, USP,ortreating patients withconcomitantantipsychotics. While immediate discontinuation oftheprevious antipsychotic treatment maybe
acceptable forsomeschizophrenic patients, moregradual discontinuation maybemostappropriate forothers. Theperiod ofoverlapping antipsychotic administration should beminimized. Whenswitching
schizophrenic patients fromdepot antipsychotics, initiate risperidone oralsolution, USPtherapy in
place ofthenextscheduled injection. Theneedforcontinuing existing EPSmedication should bere-evaluated periodically.2.2 Bipolar ManiaUsual DoseAdultsRisperidone oralsolution, USPshould beadministered onaonce-daily schedule, starting with2mgto3mg perday.Dosage adjustments, ifindicated, should occur atintervals ofnotlessthan24hours andin
dosage increments/decrements of1mgperday,asstudied intheshort-term, placebo-controlled trials. In
these trials, short-term (3week) anti-manic efficacy wasdemonstrated inaflexible dosage range of1to
6 mgperday.Risperidone oralsolution, USPdoses higher than6mgperdaywerenotstudied.[seeClinical Studies (14.2,14.3)]PediatricsThe dosage ofrisperidone oralsolution, USPshould beinitiated at0.5mgoncedaily, administered asa
single-daily doseineither themorning orevening. Dosage adjustments, ifindicated, should occur at
intervals notlessthan24hours, inincrements of0.5or1mg/day, astolerated, toarecommended doseof 2.5mg/day. Although efficacy hasbeendemonstrated instudies ofpediatric patients withbipolarmania atdoses between 0.5and6mg/day, noadditional benefit wasseenabove 2.5mg/day, andhigherdoses wereassociated withmoreadverse events. Doses higher than6mg/day havenotbeenstudied.Patients experiencing persistent somnolence maybenefit fromadministering halfthedaily dosetwicedaily.Maintenance TherapyThere isnobodyofevidence available fromcontrolled trials toguide aclinician inthelonger-term
management ofapatient whoimproves during treatment ofanacute manic episode withrisperidone oralsolution, USP.While itisgenerally agreed thatpharmacological treatment beyond anacute response inmania isdesirable, bothformaintenance oftheinitial response andforprevention ofnewmanic
episodes, there arenosystematically obtained datatosupport theuseofrisperidone oralsolution, USP
in suchlonger-term treatment (i.e., beyond 3weeks). Thephysician whoelects touserisperidone oralsolution, USPforextended periods should periodically re-evaluate thelong-term risks andbenefits of
the drugfortheindividual patient.2.3 Irritability Associated withAutistic Disorder –Pediatrics (Children andAdolescents)The safety andeffectiveness ofrisperidone oralsolution, USPinpediatric patients withautisticdisorder lessthan5years ofagehavenotbeenestablished.The dosage ofrisperidone oralsolution, USPshould beindividualized according totheresponse and
tolerability ofthepatient. Thetotal daily doseofrisperidone oralsolution, USPcanbeadministered
once daily, orhalfthetotal daily dosecanbeadministered twice daily.Dosing should beinitiated at0.25mgperdayforpatients <20kgand0.5mgperdayforpatients ≥20
kg. After aminimum offourdaysfromtreatment initiation, thedosemaybeincreased tothe
recommended doseof0.5mgperdayforpatients <20kgand1mgperdayforpatients ≥20kg.Thisdose should bemaintained foraminimum of14days. Inpatients notachieving sufficient clinicalresponse, doseincreases maybeconsidered at≥2-week intervals inincrements of0.25mgperdayforpatients <20kgor0.5mgperdayforpatients ≥20kg.Caution should beexercised withdosage forsmaller children whoweigh lessthan15kg.In clinical trials, 90%ofpatients whoshowed aresponse (based onatleast 25%improvement onABC-I,)received doses ofrisperidone oralsolution, USPbetween 0.5mgand2.5mgperday.Themaximum
daily doseofrisperidone oralsolution, USPinoneofthepivotal trials, whenthetherapeutic effectreached plateau, was1mginpatients <20kg,2.5mginpatients ≥20kg,or3mginpatients >45kg.No
dosing dataisavailable forchildren whoweighed lessthan15kg.[seeClinical Studies (14.4)]Once sufficient clinical response hasbeenachieved andmaintained, consideration should begiven to
gradually lowering thedosetoachieve theoptimal balance ofefficacy andsafety. Thephysician who
elects touserisperidone oralsolution, USPforextended periods should periodically re-evaluate the
long-term risks andbenefits ofthedrugfortheindividual patient.Patients experiencing persistent somnolence maybenefit fromaonce-daily doseadministered atbedtimeor administering halfthedaily dosetwice daily, orareduction ofthedose.2.4 Dosage inSpecial PopulationsThe recommended initial doseis0.5mgtwice daily inpatients whoareelderly ordebilitated, patientswith severe renal orhepatic impairment, andpatients either predisposed tohypotension orforwhom
hypotension would posearisk. Dosage increases inthese patients should beinincrements ofnomore
than 0.5mgtwice daily. Increases todosages above 1.5mgtwice daily should generally occur at
intervals ofatleast 1week. Insomepatients, slower titration maybemedically appropriate.Elderly ordebilitated patients, andpatients withrenal impairment, mayhavelessability toeliminate
risperidone oralsolution, USPthannormal adults. Patients withimpaired hepatic function mayhave
increases inthefreefraction ofrisperidone, possibly resulting inanenhanced effect .Patients withapredisposition tohypotensive reactions orforwhomsuchreactions would poseaparticular risk
likewise needtobetitrated cautiously andcarefully monitored .Ifaonce-daily dosing regimen inthe
elderly ordebilitated patient isbeing considered, itisrecommended thatthepatient betitrated ona
twice-daily regimen for2to3daysatthetarget dose. Subsequent switches toaonce-daily dosing
regimen canbedonethereafter. [seeClinical Pharmacology (12.3)][seeWarnings andPrecautions
(5.2,5.7,5.17)]2.5 Co-Administration ofRisperidone OralSolution withCertain Other MedicationsCo-administration ofcarbamazepine andother enzyme inducers (e.g., phenytoin, rifampin, phenobarbital)with risperidone oralsolution, USPwould beexpected tocause decreases intheplasma concentrationsof thesumofrisperidone and9-hydroxyrisperidone combined, which could leadtodecreased efficacy
of risperidone oralsolution, USPtreatment. Thedoseofrisperidone oralsolution, USPneeds tobe
titrated accordingly forpatients receiving these enzyme inducers, especially during initiation ordiscontinuation oftherapy withthese inducers [seeDrug Interactions (7.11)].Fluoxetine andparoxetine havebeenshown toincrease theplasma concentration ofrisperidone 2.5to
2.8 foldand3to9fold, respectively. Fluoxetine didnotaffect theplasma concentration of9-hydroxyrisperidone. Paroxetine lowered theconcentration of9-hydroxyrisperidone byabout 10%.Thedose ofrisperidone oralsolution, USPneeds tobetitrated accordingly whenfluoxetine orparoxetine
is co-administered [seeDrug Interactions (7.10)].2.6 Administration ofRisperidone OralSolutionRisperidone oralsolution, USPcanbeadministered directly fromthecalibrated pipette, orcanbemixedwith abeverage prior toadministration. Risperidone oralsolution, USPiscompatible inthefollowing
beverages: water, coffee, orange juice, andlow-fat milk; itisNOTcompatible witheither colaortea.3 DOSAGE FORMS &STRENGTHSRisperidone oralsolution, USPisavailable ina1mg/mL strength.4 CONTRAINDICATIONSHypersensitivity reactions, including anaphylactic reactions andangioedema, havebeenobserved in
patients treated withrisperidone. Therefore, risperidone iscontraindicated inpatients withaknown
hypersensitivity totheproduct.5 WARNINGS ANDPRECAUTIONS
5.1 Increased Mortality inElderly Patients withDementia-Related PsychosisElderly patients withdementia-related psychosis treated withantipsychotic drugs areatanincreased
risk ofdeath. Risperidone isnotapproved forthetreatment ofdementia-related psychosis .[seeBoxedWarning]5.2 Cerebrovascular Adverse Events, Including Stroke, inElderly Patients withDementia-RelatedPsychosisCerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were
reported inpatients (mean age85years; range 73to97)intrials ofrisperidone inelderly patients with
dementia-related psychosis. Inplacebo-controlled trials, there wasasignificantly higher incidence ofcerebrovascular adverse events inpatients treated withrisperidone compared topatients treated with
placebo. Risperidone isnotapproved forthetreatment ofpatients withdementia-related psychosis. [SeealsoBoxed WarningsandWarnings andPrecautions (5.1)]5.3 Neuroleptic Malignant Syndrome (NMS)A potentially fatal symptom complex sometimes referred toasNeuroleptic Malignant Syndrome (NMS)has beenreported inassociation withantipsychotic drugs. Clinical manifestations ofNMSarehyperpyrexia, muscle rigidity, altered mental status, andevidence ofautonomic instability (irregularpulse orblood pressure, tachycardia, diaphoresis, andcardiac dysrhythmia). Additional signs may
include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), andacute renal failure.The diagnostic evaluation ofpatients withthissyndrome iscomplicated. Inarriving atadiagnosis, itis
important toidentify cases inwhich theclinical presentation includes bothserious medical illness (e.g.,pneumonia, systemic infection, etc.) anduntreated orinadequately treated extrapyramidal signs and
symptoms (EPS). Other important considerations inthedifferential diagnosis include centralanticholinergic toxicity, heatstroke, drugfever, andprimary central nervous system pathology.The management ofNMSshould include: (1)immediate discontinuation ofantipsychotic drugs andotherdrugs notessential toconcurrent therapy; (2)intensive symptomatic treatment andmedical monitoring;and (3)treatment ofanyconcomitant serious medical problems forwhich specific treatments are
available. There isnogeneral agreement about specific pharmacological treatment regimens foruncomplicated NMS.If apatient requires antipsychotic drugtreatment after recovery fromNMS,thepotential reintroduction
of drugtherapy should becarefully considered. Thepatient should becarefully monitored, since
recurrences ofNMShavebeenreported.5.4 Tardive DyskinesiaA syndrome ofpotentially irreversible, involuntary, dyskinetic movements maydevelop inpatients
treated withantipsychotic drugs. Although theprevalence ofthesyndrome appears tobehighest among
the elderly, especially elderly women, itisimpossible torelyuponprevalence estimates topredict, at
the inception ofantipsychotic treatment, which patients arelikely todevelop thesyndrome. Whetherantipsychotic drugproducts differ intheir potential tocause tardive dyskinesia isunknown.The riskofdeveloping tardive dyskinesia andthelikelihood thatitwillbecome irreversible arebelieved toincrease astheduration oftreatment andthetotal cumulative doseofantipsychotic drugsadministered tothepatient increase. However, thesyndrome candevelop, although muchlesscommonly, after relatively brief treatment periods atlowdoses.There isnoknown treatment forestablished cases oftardive dyskinesia, although thesyndrome may
remit, partially orcompletely, ifantipsychotic treatment iswithdrawn. Antipsychotic treatment, itself,however, maysuppress (orpartially suppress) thesigns andsymptoms ofthesyndrome andthereby may
possibly masktheunderlying process. Theeffect thatsymptomatic suppression hasuponthelong-term
course ofthesyndrome isunknown.Given these considerations, risperidone should beprescribed inamanner thatismostlikely tominimize
the occurrence oftardive dyskinesia. Chronic antipsychotic treatment should generally bereserved forpatients whosuffer fromachronic illness that: (1)isknown torespond toantipsychotic drugs, and(2)
for whomalternative, equally effective, butpotentially lessharmful treatments arenotavailable orappropriate. Inpatients whodorequire chronic treatment, thesmallest doseandtheshortest duration of
treatment producing asatisfactory clinical response should besought. Theneedforcontinued treatmentshould bereassessed periodically.If signs andsymptoms oftardive dyskinesia appear inapatient treated withrisperidone, drug
discontinuation should beconsidered. However, somepatients mayrequire treatment withrisperidonedespite thepresence ofthesyndrome.5.5 Hyperglycemia andDiabetes MellitusHyperglycemia anddiabetes mellitus, insomecases extreme andassociated withketoacidosis orhyperosmolar comaordeath, havebeenreported inpatients treated withatypical antipsychotics
including risperidone. Assessment oftherelationship between atypical antipsychotic useandglucose
abnormalities iscomplicated bythepossibility ofanincreased background riskofdiabetes mellitus in
patients withschizophrenia andtheincreasing incidence ofdiabetes mellitus inthegeneral population.Given these confounders, therelationship between atypical antipsychotic useandhyperglycemia-related adverse events isnotcompletely understood. However, epidemiological studies suggest an
increased riskoftreatment-emergent hyperglycemia-related adverse events inpatients treated withthe
atypical antipsychotics. Precise riskestimates forhyperglycemia-related adverse events inpatients
treated withatypical antipsychotics arenotavailable.Patients withanestablished diagnosis ofdiabetes mellitus whoarestarted onatypical antipsychotics,including risperidone, should bemonitored regularly forworsening ofglucose control. Patients with
risk factors fordiabetes mellitus (e.g., obesity, family history ofdiabetes) whoarestarting treatmentwith atypical antipsychotics, including risperidone, should undergo fasting blood glucose testing atthebeginning oftreatment andperiodically during treatment. Anypatient treated withatypicalantipsychotics, including risperidone, should bemonitored forsymptoms ofhyperglycemia including
polydipsia, polyuria, polyphagia, andweakness. Patients whodevelop symptoms ofhyperglycemiaduring treatment withatypical antipsychotics, including risperidone, should undergo fasting blood
glucose testing. Insomecases, hyperglycemia hasresolved whentheatypical antipsychotic, including
risperidone oralsolution, wasdiscontinued; however, somepatients required continuation ofanti-diabetic treatment despite discontinuation ofrisperidone.5.6 HyperprolactinemiaAs withother drugs thatantagonize dopamine Dreceptors, risperidone elevates prolactin levels andthe
elevation persists during chronic administration. Risperidone isassociated withhigher levels ofprolactin elevation thanother antipsychotic agents. Hyperprolactinemia maysuppress hypothalamic GnRH, resulting inreduced pituitary gonadotropin
secretion. This, inturn, mayinhibit reproductive function byimpairing gonadal steroidogenesis inboth
female andmalepatients. Galactorrhea, amenorrhea, gynecomastia, andimpotence havebeenreported in
patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia whenassociatedwith hypogonadism mayleadtodecreased bonedensity inbothfemale andmalesubjects.Tissue culture experiments indicate thatapproximately one-third ofhuman breast cancers areprolactin
dependent ,afactor ofpotential importance iftheprescription ofthese drugs iscontemplated inapatientwith previously detected breast cancer. Anincrease inpituitary gland, mammary gland, andpancreatic
islet cellneoplasia (mammary adenocarcinomas, pituitary andpancreatic adenomas) wasobserved inthe
risperidone carcinogenicity studies conducted inmiceandrats.Neither clinical studies norepidemiologic studies conducted todatehaveshown anassociation between chronic administration of
this class ofdrugs andtumorigenesis inhumans; theavailable evidence isconsidered toolimited tobe
conclusive atthistime. invitro[see Non-Clinical Toxicology (13.1)]5.7 Orthostatic HypotensionRisperidone mayinduce orthostatic hypotension associated withdizziness, tachycardia, andinsomepatients, syncope, especially during theinitial dose-titration period, probably reflecting itsalpha-adrenergic antagonistic properties. Syncope wasreported in0.2%(6/2607) ofrisperidone-treated
patients inPhase 2and3studies inadults withschizophrenia. Theriskoforthostatic hypotension and
syncope maybeminimized bylimiting theinitial doseto2mgtotal (either oncedaily or1mgtwicedaily) innormal adults and0.5mgtwice daily intheelderly andpatients withrenal orhepatic impairment
. Monitoring oforthostatic vital signs should beconsidered inpatients forwhomthisisofconcern. A
dose reduction should beconsidered ifhypotension occurs. Risperidone should beusedwithparticularcaution inpatients withknown cardiovascular disease (history ofmyocardial infarction orischemia,heart failure, orconduction abnormalities), cerebrovascular disease, andconditions which would
predispose patients tohypotension, e.g., dehydration andhypovolemia. Clinically significanthypotension hasbeenobserved withconcomitant useofrisperidone andantihypertensive medication.[seeDosage andAdministration (2.1,2.4)]5.8 Leukopenia, Neutropenia, andAgranulocytosis
In clinical trial and/or postmarketing experience, events ofleukopenia/neutropenia havebeenreported
temporally related toantipsychotic agents, including risperidone. Agranulocytosis hasalsobeen
reported. Class Effect:Possible riskfactors forleukopenia/neutropenia include pre-existing lowwhite blood cellcount(WBC) andhistory ofdrug-induced leukopenia/neutropenia. Patients withahistory ofaclinically
significant lowWBCoradrug-induced leukopenia/neutropenia should havetheir complete blood count(CBC) monitored frequently during thefirst fewmonths oftherapy anddiscontinuation ofrisperidone
should beconsidered atthefirst signofaclinically significant decline inWBCintheabsence ofothercausative factors.Patients withclinically significant neutropenia should becarefully monitored forfever orothersymptoms orsigns ofinfection andtreated promptly ifsuchsymptoms orsigns occur. Patients with
severe neutropenia (absolute neutrophil count <1000/mm)should discontinue risperidone andhave
their WBCfollowed until recovery. 5.9 Potential forCognitive andMotor ImpairmentSomnolence wasacommonly reported adverse event associated withrisperidone treatment, especiallywhen ascertained bydirect questioning ofpatients. Thisadverse event isdose-related, andinastudy
utilizing achecklist todetect adverse events, 41%ofthehigh-dose patients (risperidone 16mg/day)
reported somnolence compared to16%ofplacebo patients. Direct questioning ismoresensitive fordetecting adverse events thanspontaneous reporting, bywhich 8%ofrisperidone 16mg/day patientsand 1%ofplacebo patients reported somnolence asanadverse event. Since risperidone hasthepotential
to impair judgment, thinking, ormotor skills, patients should becautioned about operating hazardousmachinery, including automobiles, until theyarereasonably certain thatrisperidone therapy doesnotaffect themadversely.5.10 SeizuresDuring premarketing testing inadult patients withschizophrenia, seizures occurred in0.3%(9/2607) of
risperidone-treated patients, twoinassociation withhyponatremia. Risperidone should beused
cautiously inpatients withahistory ofseizures.5.11 DysphagiaEsophageal dysmotility andaspiration havebeenassociated withantipsychotic druguse.Aspiration
pneumonia isacommon cause ofmorbidity andmortality inpatients withadvanced Alzheimer’sdementia. Risperidone andother antipsychotic drugs should beusedcautiously inpatients atriskforaspiration pneumonia. [SeealsoBoxed WarningandWarnings andPrecautions (5.1)]5.12 Priapism
Priapism hasbeenreported during postmarketing surveillance .Severe priapism mayrequire surgical
intervention. [seeAdverse Reactions (6.9)]5.13 Thrombotic Thrombocytopenic Purpura (TTP)A single caseofTTPwasreported ina28year-old female patient receiving risperidone inalarge,open premarketing experience (approximately 1300patients). Sheexperienced jaundice, fever, and
bruising, buteventually recovered after receiving plasmapheresis. Therelationship torisperidone
therapy isunknown.5.14 BodyTemperature RegulationDisruption ofbodytemperature regulation hasbeenattributed toantipsychotic agents. Both
hyperthermia andhypothermia havebeenreported inassociation withoralrisperidone use.Caution isadvised whenprescribing forpatients whowillbeexposed totemperature extremes.5.15 Antiemetic EffectRisperidone hasanantiemetic effect inanimals; thiseffect mayalsooccur inhumans, andmaymask
signs andsymptoms ofoverdosage withcertain drugs orofconditions suchasintestinal obstruction,Reye’s syndrome, andbrain tumor.5.16 SuicideThe possibility ofasuicide attempt isinherent inpatients withschizophrenia andbipolar mania,including children andadolescent patients, andclose supervision ofhigh-risk patients should
accompany drugtherapy. Prescriptions forrisperidone should bewritten forthesmallest amount,consistent withgoodpatient management, inorder toreduce theriskofoverdose.5.17 UseinPatients withConcomitant IllnessClinical experience withrisperidone inpatients withcertain concomitant systemic illnesses islimited.Patients withParkinson’s Disease orDementia withLewyBodies whoreceive antipsychotics,including risperidone, arereported tohaveanincreased sensitivity toantipsychotic medications.Manifestations ofthisincreased sensitivity havebeenreported toinclude confusion, obtundation,postural instability withfrequent falls, extrapyramidal symptoms, andclinical features consistent with
the neuroleptic malignant syndrome.Caution isadvisable inusing risperidone inpatients withdiseases orconditions thatcould affectmetabolism orhemodynamic responses. Risperidone hasnotbeenevaluated orusedtoanyappreciable
extent inpatients witharecent history ofmyocardial infarction orunstable heart disease. Patients with
these diagnoses wereexcluded fromclinical studies during theproduct's premarket testing.Increased plasma concentrations ofrisperidone and9-hydroxyrisperidone occur inpatients withsevere
renal impairment (creatinine clearance <30mL/min/1.73 m),andanincrease inthefreefraction of
risperidone isseeninpatients withsevere hepatic impairment. Alower starting doseshould beusedin
such patients .[seeDosage andAdministration (2.4)]5.18 Monitoring: Laboratory TestsNo specific laboratory tests arerecommended.6 ADVERSE REACTIONSThe following arediscussed inmoredetail inother sections ofthelabeling:•
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•The mostcommon adverse reactions inclinical trials (≥10%)weresomnolence, increased appetite,fatigue, insomnia, sedation, parkinsonism, akathisia, vomiting, cough, constipation, nasopharyngitis,drooling, rhinorrhea, drymouth, abdominal painupper, dizziness, nausea, anxiety, headache, nasalcongestion, rhinitis, tremor, andrash.The mostcommon adverse reactions thatwereassociated withdiscontinuation fromclinical trials
(causing discontinuation in>1%ofadults and/or >2%ofpediatrics) werenausea, somnolence, sedation,vomiting, dizziness, andakathisia .[seeAdverse Reactions (6.5)]The datadescribed inthissection arederived fromaclinical trial database consisting of9712adult and
pediatric patients exposed tooneormoredoses ofrisperidone forthetreatment ofschizophrenia,bipolar mania, autistic disorder, andother psychiatric disorders inpediatrics andelderly patients with
dementia. Ofthese 9712patients, 2626werepatients whoreceived risperidone while participating in
double-blind, placebo-controlled trials. Theconditions andduration oftreatment withrisperidonevaried greatly andincluded (inoverlapping categories) double-blind, fixed- andflexible-dose, placebo-or active-controlled studies andopen-label phases ofstudies, inpatients andoutpatients, andshort-term
(up to12weeks) andlonger-term (upto3years) exposures. Safety wasassessed bycollecting adverse
events andperforming physical examinations, vital signs, bodyweights, laboratory analyses, andECGs.Adverse events during exposure tostudy treatment wereobtained bygeneral inquiry andrecorded by
clinical investigators using their ownterminology. Consequently, toprovide ameaningful estimate of
the proportion ofindividuals experiencing adverse events, events weregrouped instandardized
categories using MedDRA terminology.Throughout thissection, adverse reactions arereported. Adverse reactions areadverse events thatwere considered tobereasonably associated withtheuseofrisperidone (adverse drugreactions) based
on thecomprehensive assessment oftheavailable adverse event information. Acausal association for
risperidone often cannot bereliably established inindividual cases. Further, because clinical trials are
conducted under widely varying conditions, adverse reaction rates observed intheclinical trials ofadrug cannot bedirectly compared torates intheclinical trials ofanother drugandmaynotreflect the
rates observed inclinical practice.The majority ofalladverse reactions weremildtomoderate inseverity.6.1 Commonly-Observed Adverse Reactions inDouble-Blind, Placebo-Controlled Clinical Trials -SchizophreniaAdult Patients withSchizophreniaTable 1lists theadverse reactions reported in1%ormoreofrisperidone-treated adult patients with
schizophrenia inthree 4-to8-week, double-blind, placebo-controlled trials.Table 1.Adverse Reactions in≥1%ofRisperidone-Treated Adult Patients with
Schizophrenia inDouble-Blind, Placebo-Controlled TrialsPercentage ofPatients Reporting EventRisperidoneAdverse ReactionSystem/Organ Class2 to8mgperday(N=366)>8 to16mgperday(N=198)Placebo(N=225)Blood andLymphatic SystemDisordersAnemia<110Cardiac DisordersTachycardia130Ear andLabyrinth DisordersEar pain<110Eye DisordersVision blurred311Gastrointestinal DisordersNausea944Constipation896Dyspepsia865Vomiting757Dry mouth401Abdominal discomfort311Salivary hypersecretion21<1Diarrhea211Abdominal pain110Abdominal painupper110Stomach discomfort111General DisordersFatigue310Chest pain221Asthenia21<1
Immune System DisordersHypersensitivity<110
Infections andInfestationsNasopharyngitis343Upper respiratory tract
infection
231Sinusitis121Urinary tract infection130
InvestigationsWeight increased110Blood creatinephosphokinase increased
12<1Heart rateincreased<120Metabolism andNutrition DisordersDecreased appetite10<1Musculoskeletal andConnectiveTissue DisordersBack pain411Arthralgia23<1Pain inextremity211
Joint stiffness110Nervous System DisordersParkinsonism*14178Akathisia*10103Dizziness742Somnolence721Dystonia*342Sedation331Tremor*231Dizziness postural200Dyskinesia*122Syncope110Psychiatric Disorders
Insomnia322527Anxiety161111Nervousness11<1Renal andUrinary DisordersUrinary incontinence110Reproductive System andBreastDisordersEjaculation failure<110Respiratory, Thoracic andMediastinal DisordersNasal congestion462Dyspnea120Epistaxis<120Skin andSubcutaneous TissueDisordersRash141Dry skin130Dandruff110Seborrheic dermatitis<110Hyperkeratosis011Vascular DisordersOrthostatic hypotension210Hypotension110Pediatric Patients withSchizophreniaTable 2lists theadverse reactions reported in5%ormoreofrisperidone-treated pediatric patients with
schizophrenia ina6-week double-blind, placebo-controlled trial.Table 2.Adverse Reactions in≥5%ofRisperidone-Treated Pediatric Patientswith Schizophrenia inaDouble-Blind TrialPercentage ofPatients Reporting EventRisperidoneAdverse ReactionSystem/Organ Class1 to3mgperday(N=55)4 to6mgperday(N=51)Placebo(N=54)Gastrointestinal DisordersSalivary hypersecretion0102Nervous System DisordersParkinsonism*162811Sedation1382Somnolence1142Tremor11106Akathisia*9104Dizziness7142Dystonia*260Psychiatric DisordersAnxiety760
6.2 Commonly-Observed Adverse Reactions inDouble-Blind, Placebo-Controlled Clinical Trials –BipolarManiaAdult Patients withBipolar ManiaTable 3lists theadverse reactions reported in1%ormoreofrisperidone-treated adult patients with
bipolar mania infour3-week, double-blind, placebo-controlled monotherapy trials.Table 3.Adverse Reactions in≥1%ofRisperidone-Treated Adult Patients withBipolar Mania inDouble-Blind, Placebo-Controlled Monotherapy TrialsPercentage ofPatients Reporting EventAdverse ReactionSystem/Organ ClassRisperidone 1to6mgperday(N=448)Placebo(N=424)Cardiac DisordersTachycardia1<1Eye DisordersVision blurred21Gastrointestinal DisordersNausea52Diarrhea32Salivary hypersecretion31Dyspepsia22Stomach discomfort2<1General DisordersFatigue21Asthenia11Pyrexia11
Infections andInfestationsNasopharyngitis11
InvestigationsAspartate aminotransferase
increased
1<1Nervous System DisordersParkinsonism*259Akathisia*93Tremor*63Dizziness65Sedation62Somnolence52Dystonia*51Lethargy21Dyskinesia*1<1Reproductive System andBreastDisordersGalactorrhea10Skin andSubcutaneous TissueDisordersAcne10Table 4lists theadverse reactions reported in2%ormoreofrisperidone-treated adult patients with
bipolar mania intwo3-week, double-blind, placebo-controlled adjuvant therapy trials.Table 4.Adverse Reactions in≥2%ofRisperidone-Treated Adult Patients withBipolar Mania inDouble-Blind, Placebo-Controlled Adjuvant Therapy TrialsPercentage ofPatients Reporting EventSystem/Organ ClassRisperidone +MoodStabilizerPlacebo +MoodStabilizerAdverse Reaction(N=127)(N=126)Cardiac DisordersPalpitations20Gastrointestinal DisordersDyspepsia98Nausea64Diarrhea64Dry mouth44Vomiting46Constipation33Salivary hypersecretion20General DisordersChest pain21Fatigue22
Infections andInfestationsNasopharyngitis23Urinary tract infection21
InvestigationsWeight increased22Nervous System DisordersParkinsonism*144Headache1415Akathisia*80Dizziness72Sedation63Tremor62Somnolence31Lethargy21Psychiatric Disorders
Insomnia48Anxiety32Respiratory, Thoracic andMediastinal DisordersPharyngolaryngeal pain52Cough20Pediatric Patients withBipolar ManiaTable 5lists theadverse reactions reported in5%ormoreofrisperidone-treated pediatric patients with
bipolar mania ina3-week double-blind, placebo-controlled trial.Table 5.Adverse Reactions in≥5%ofRisperidone-Treated Pediatric Patientswith Bipolar Mania inDouble-Blind, Placebo-Controlled TrialsPercentage ofPatients Reporting EventRisperidoneAdverse ReactionSystem/Organ Class0.5 to2.5mgperday(N=50)3 to6mgperday(N=61)Placebo(N=58)Eye DisordersVision blurred470Gastrointestinal DisordersAbdominal painupper16135Nausea16137Vomiting10105Diarrhea872Dyspepsia1032Stomach discomfort602General DisordersFatigue18303Metabolism andNutrition Disorders
Increased appetite472Nervous System DisordersSomnolence223012Sedation20237Dizziness16135Parkinsonism*6123Dystonia*650Akathisia*082Psychiatric DisordersAnxiety083Respiratory, Thoracic andMediastinal DisordersPharyngolaryngeal pain1035Skin andSubcutaneous Tissue DisordersRash072
6.3 Commonly-Observed Adverse Reactions inDouble-Blind, Placebo-Controlled Clinical Trials -AutisticDisorderTable 6lists theadverse reactions reported in5%ormoreofrisperidone-treated pediatric patients
treated forirritability associated withautistic disorder intwo8-week, double-blind, placebo-controlled
trials.Table 6.Adverse Reactions in≥5%ofRisperidone-Treated Pediatric PatientsTreated forIrritability Associated withAutistic Disorder inDouble-Blind, Placebo-Controlled TrialsPercentage ofPatients Reporting EventAdverse Reaction System/OrganClassRisperidone 0.5to4.0mgperday(N=76)Placebo(N=80)Cardiac DisordersTachycardia50Gastrointestinal DisordersVomiting2521Constipation218Dry mouth156Salivary hypersecretion90Nausea86General DisordersFatigue4213Feeling abnormal50
Infections andInfestationsNasopharyngitis2110Rhinitis1310Upper respiratory tract infection83
InvestigationsWeight increased50Metabolism andNutrition Disorders
Increased appetite4719Nervous System DisordersSomnolence4918Sedation293Drooling165Tremor121Parkinsonism*111Dizziness93Dyskinesia73Lethargy53Respiratory, Thoracic andMediastinal DisordersCough2418Rhinorrhea1613Nasal congestion135Skin andSubcutaneous Tissue DisordersRash118
6.4 Other Adverse Reactions Observed During thePremarketing Evaluation ofRisperidoneThe following adverse reactions occurred in<1%oftheadult patients andin<5%ofthepediatricpatients treated withrisperidone intheabove double-blind, placebo-controlled clinical trial datasets. In
addition, thefollowing alsoincludes adverse reactions reported inrisperidone-treated patients who
participated inother studies, including double-blind, active-controlled andopen-label studies in
schizophrenia andbipolar mania studies inpediatric patients withpsychiatric disorders other than
schizophrenia, bipolar mania, orautistic disorder, andstudies inelderly patients withdementia.Blood andLymphatic System Disorders: granulocytopeniaCardiac Disorders: sinus bradycardia, sinus tachycardia, atrioventricular block first degree, bundlebranch block left, bundle branch block right, atrioventricular blockEar andLabyrinth Disorders: tinnitusEndocrine Disorders: hyperprolactinemiaEye Disorders: ocular hyperemia, eyedischarge, conjunctivitis, eyerolling, eyelid edema, eye
swelling, eyelid margin crusting, dryeye,lacrimation increased, photophobia, glaucoma, visual acuity
reducedGastrointestinal Disorders: dysphagia, fecaloma, fecal incontinence, gastritis, lipswelling, cheilitis,aptyalism
General Disorders: edema peripheral, thirst, gaitdisturbance, influenza-like illness, pitting edema,edema, chills, sluggishness, malaise, chest discomfort, faceedema, discomfort, generalized edema,drug withdrawal syndrome, peripheral coldness
Immune System Disorders: drughypersensitivity
Infections andInfestations: pneumonia, influenza, earinfection, viral infection, pharyngitis, tonsillitis,bronchitis, eyeinfection, localized infection, cystitis, cellulitis, otitis media, onychomycosis,acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic
Investigations: bodytemperature increased, blood prolactin increased, alanine aminotransferase
increased, electrocardiogram abnormal, eosinophil count increased, white blood cellcount decreased,blood glucose increased, hemoglobin decreased, hematocrit decreased, bodytemperature decreased,blood pressure decreased, transaminases increasedMetabolism andNutrition Disorders: polydipsia, anorexiaMusculoskeletal andConnective Tissue Disorders: joint swelling, musculoskeletal chest pain, posture
abormal, myalgia, neckpain, muscular weakness, rhabdomyolysisNervous System Disorders: balance disorder, disturbance inattention, dysarthria, unresponsive to
stimuli, depressed level ofconsciousness, movement disorder, hypersomnia, transient ischemic attack,coordination abnormal, cerebrovascular accident, speech disorder, lossofconsciousness,hypoesthesia, tardive dyskinesia, cerebral ischemia, cerebrovascular disorder, neuroleptic malignantsyndrome, diabetic comaPsychiatric Disorders: agitation, blunted affect, confusional state, middle insomnia, sleep disorder,listless, libido decreased, anorgasmiaRenal andUrinary Disorders: enuresis, dysuria, pollakiuriaReproductive System andBreast Disorders: menstruation irregular, amenorrhea, gynecomastia, vaginaldischarge, menstrual disorder, erectile dysfunction, retrograde ejaculation, ejaculation disorder, sexualdysfunction, breast enlargementRespiratory, Thoracic, andMediastinal Disorders: wheezing, pneumonia aspiration, sinus congestion,dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory
disorder, hyperventilation, nasal edemaSkin andSubcutaneous Tissue Disorders: erythema, skindiscoloration, skinlesion, pruritus, skin
disorder, rasherythematous, rashpapular, rashgeneralized, rashmaculopapularVascular Disorders: flushing
6.5 Discontinuations DuetoAdverse ReactionsSchizophrenia -AdultsApproximately 7%(39/564) ofrisperidone-treated patients indouble-blind, placebo-controlled trialsdiscontinued treatment duetoanadverse event, compared with4%(10/225) whowerereceiving
placebo. Theadverse reactions associated withdiscontinuation in2ormorerisperidone-treated patientswere:Table 7.Adverse Reactions Associated WithDiscontinuation in2orMoreRisperidone-Treated Adult Patients inSchizophrenia TrialsRisperidoneAdverse Reaction
2 to8mg/day
(N=366)>8 to16mg/day
(N=198)Placebo(N=225)Dizziness1.4%1.0%0%
Nausea1.4%0%0%
Vomiting0.8%0%0%
Parkinsonism0.8%0%0%
Somnolence0.8%0%0%
Dystonia0.5%0%0%
Agitation0.5%0%0%
Abdominal pain0.5%0%0%
Orthostatichypotension
0.3%0.5%0%
Akathisia0.3%2.0%0%
Discontinuation forextrapyramidal symptoms (including Parkinsonism, akathisia, dystonia, andtardivedyskinesia) was1%inplacebo-treated patients, and3.4%inactive control-treated patients inadouble-blind, placebo- andactive-controlled trial.Schizophrenia -PediatricsApproximately 7%(7/106), ofrisperidone-treated patients discontinued treatment duetoanadverse
event inadouble-blind, placebo-controlled trial, compared with4%(2/54) placebo-treated patients. The
adverse reactions associated withdiscontinuation foratleast onerisperidone-treated patient weredizziness (2%), somnolence (1%), sedation (1%), lethargy (1%), anxiety (1%), balance disorder (1%),hypotension (1%), andpalpitation (1%).Bipolar Mania -Adults
In double-blind, placebo-controlled trials withrisperidone asmonotherapy, approximately 6%(25/448)of risperidone-treated patients discontinued treatment duetoanadverse event, compared with
approximately 5%(19/424) ofplacebo-treated patients. Theadverse reactions associated with
discontinuation inrisperidone-treated patients were:Table 8.Adverse Reactions Associated WithDiscontinuation in2orMoreRisperidone-Treated Adult Patients inBipolar Mania Clinical TrialsAdverse ReactionRisperidone 1to6mg/day(N=448)Placebo(N=424)Parkinsonism0.4%0%
Lethargy0.2%0%
Dizziness0.2%0%
Alanine aminotransferase
increased
0.2%0.2%
Aspartate aminotransferase
increased
0.2%0.2%
Bipolar Mania -Pediatrics
In adouble-blind, placebo-controlled trial 12%(13/111) ofrisperidone-treated patients discontinued
due toanadverse event, compared with7%(4/58) ofplacebo-treated patients. Theadverse reactionsassociated withdiscontinuation inmorethanonerisperidone-treated pediatric patient werenausea (3%),somnolence (2%), sedation (2%), andvomiting (2%).Autistic Disorder -Pediatrics
In thetwo8-week, placebo-controlled trials inpediatric patients treated forirritability associated with
autistic disorder (n=156), onerisperidone-treated patient discontinued duetoanadverse reaction
(Parkinsonism), andoneplacebo-treated patient discontinued duetoanadverse event.6.6 DoseDependency ofAdverse Reactions inClinical TrialsExtrapyramidal SymptomsData fromtwofixed-dose trials inadults withschizophrenia provided evidence ofdose-relatedness forextrapyramidal symptoms associated withrisperidone treatment.Two methods wereusedtomeasure extrapyramidal symptoms (EPS) inan8-week trial comparing 4
fixed doses ofrisperidone (2,6,10,and16mg/day), including (1)aParkinsonism score (mean change
from baseline) fromtheExtrapyramidal Symptom Rating Scale, and(2)incidence ofspontaneouscomplaints ofEPS:Dose GroupsPlaceboRisperidone2mgRisperidone6mgRisperidone10mgRisperidone16 mgParkinsonism1.20.91.82.42.6EPS
Incidence13%17%21%21%35%
Similar methods wereusedtomeasure extrapyramidal symptoms (EPS) inan8-week trial comparing 5
fixed doses ofrisperidone (1,4,8,12,and16mg/day):DoseGroupsRisperidone1mgRisperidone4mgRisperidone8mgRisperidone12mgRisperidone 16mgParkinsonism0.61.72.42.94.1EPS
Incidence7%12%17%18%20%
DystoniaSymptoms ofdystonia, prolonged abnormal contractions ofmuscle groups, mayoccur insusceptible
individuals during thefirst fewdaysoftreatment. Dystonic symptoms include: spasm oftheneckmuscles, sometimes progressing totightness ofthethroat, swallowing difficulty, difficulty breathing,and/or protrusion ofthetongue. While these symptoms canoccur atlowdoses, theyoccur more
frequently andwithgreater severity withhighpotency andathigher doses offirst generation
antipsychotic drugs. Anelevated riskofacute dystonia isobserved inmales andyounger agegroups.Class Effect:Other Adverse ReactionsAdverse event dataelicited byachecklist forsideeffects fromalarge study comparing 5fixed dosesof risperidone (1,4,8,12,and16mg/day) wereexplored fordose-relatedness ofadverse events. A
Cochran-Armitage Testfortrend inthese datarevealed apositive trend (p<0.05) forthefollowing
adverse reactions: somnolence, vision abnormal, dizziness, palpitations, weight increase, erectiledysfunction, ejaculation disorder, sexual function abnormal, fatigue, andskindiscoloration.6.7 Changes inBodyWeightThe proportions ofrisperidone andplacebo-treated adult patients withschizophrenia meeting aweightgain criterion of≥7%ofbodyweight werecompared inapoolof6-to8-week, placebo-controlled
trials, revealing astatistically significantly greater incidence ofweight gainforrisperidone (18%)compared toplacebo (9%). Inapoolofplacebo-controlled 3-week studies inadult patients withacutemania, theincidence ofweight increase of≥7%atendpoint wascomparable intherisperidone (2.5%)and placebo (2.4%) groups, andwasslightly higher intheactive-control group (3.5%).Changes inbodyweight werealsoevaluated inpediatric patients [seeUse inSpecific Populations (8.4)]6.8 Changes inECG
Between-group comparisons forpooled placebo-controlled trials inadults revealed nostatistically
significant differences between risperidone andplacebo inmeanchanges frombaseline inECG
parameters, including QT,QTc,andPRintervals, andheart rate. Whenallrisperidone doses werepooled fromrandomized controlled trials inseveral indications, there wasameanincrease inheart rateof 1beatperminute compared tonochange forplacebo patients. Inshort-term schizophrenia trials,higher doses ofrisperidone (8to16mg/day) wereassociated withahigher meanincrease inheart rate
compared toplacebo (4to6beats perminute). Inpooled placebo-controlled acute mania trials inadults,there weresmall decreases inmeanheart rate, similar among alltreatment groups.In thetwoplacebo-controlled trials inchildren andadolescents withautistic disorder (aged 5to16
years) meanchanges inheart ratewereanincrease of8.4beats perminute intherisperidone groups and
6.5 beats perminute intheplacebo group. There werenoother notable ECGchanges.In aplacebo-controlled acute mania trial inchildren andadolescents (aged 10to17years), there wereno significant changes inECGparameters, other thantheeffect ofrisperidone totransiently increasepulse rate(<6beats perminute). Intwocontrolled schizophrenia trials inadolescents (aged 13to17
years), there werenoclinically meaningful changes inECGparameters including corrected QT
intervals between treatment groups orwithin treatment groups overtime.6.9 Postmarketing ExperienceThe following adverse reactions havebeenidentified during postapproval useofrisperidone; because
these reactions arereported voluntarily fromapopulation ofuncertain size, itisnotpossible toreliably
estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrialfibrillation, diabetes mellitus, diabetic ketoacidosis inpatients withimpaired glucose metabolism,hypoglycemia, hypothermia, inappropriate antidiuretic hormone secretion, intestinal obstruction,jaundice, mania, pancreatitis, priapism, QTprolongation, sleep apnea syndrome, thrombocytopenia,urinary retention, andwater intoxication.Other adverse events reported since market introduction, which weretemporally related torisperidonebut notnecessarily causally related, include thefollowing: pituitary adenoma, pulmonary embolism,precocious puberty, cardiopulmonary arrest, andsudden death.7 DRUGINTERACTIONS
7.1 Centrally-Acting Drugs andAlcoholGiven theprimary CNSeffects ofrisperidone, caution should beusedwhenrisperidone istaken in
combination withother centrally-acting drugs andalcohol.7.2 Drugs withHypotensive EffectsBecause ofitspotential forinducing hypotension, risperidone mayenhance thehypotensive effects ofother therapeutic agents withthispotential.7.3 Levodopa andDopamine AgonistsRisperidone mayantagonize theeffects oflevodopa anddopamine agonists.7.4 AmitriptylineAmitriptyline didnotaffect thepharmacokinetics ofrisperidone orrisperidone and9-hydroxyrisperidone combined.7.5 Cimetidine andRanitidineCimetidine andranitidine increased thebioavailability ofrisperidone by64%and26%,respectively.However, cimetidine didnotaffect theAUCofrisperidone and9-hydroxyrisperidone combined,whereas ranitidine increased theAUCofrisperidone and9-hydroxyrisperidone combined by20%.7.6 ClozapineChronic administration ofclozapine withrisperidone maydecrease theclearance ofrisperidone.7.7 Lithium
Repeated oraldoses ofrisperidone (3mgtwice daily) didnotaffect theexposure (AUC) orpeak
plasma concentrations (C)oflithium (n=13). 7.8 ValproateRepeated oraldoses ofrisperidone (4mgoncedaily) didnotaffect thepre-dose oraverage plasma
concentrations andexposure (AUC) ofvalproate (1000 mg/day inthree divided doses) compared to
placebo (n=21). However, there wasa20%increase invalproate peakplasma concentration (C)afterconcomitant administration ofrisperidone. 7.9 DigoxinRisperidone (0.25 mgtwice daily) didnotshowaclinically relevant effect onthepharmacokinetics ofdigoxin.7.10 Drugs ThatInhibit CYP2D6andOther CYPIsozymesRisperidone ismetabolized to9-hydroxyrisperidone byCYP2D6,anenzyme thatispolymorphic inthepopulation andthatcanbeinhibited byavariety ofpsychotropic andother drugs .Druginteractions thatreduce themetabolism ofrisperidone to9-hydroxyrisperidone would increase theplasma
concentrations ofrisperidone andlower theconcentrations of9-hydroxyrisperidone. Analysis ofclinical studies involving amodest number ofpoormetabolizers (n�70) doesnotsuggest thatpoorand
extensive metabolizers havedifferent rates ofadverse effects. Nocomparison ofeffectiveness inthe
two groups hasbeenmade. [seeClinical Pharmacology (12.3)]
studies showed thatdrugs metabolized byother CYPisozymes, including 1A1,1A2,2C9,2C19, and
3A4, areonlyweakinhibitors ofrisperidone metabolism. InvitroFluoxetine andParoxetineFluoxetine (20mgoncedaily) andparoxetine (20mgoncedaily) havebeenshown toincrease theplasma concentration ofrisperidone 2.5to2.8foldand3to9fold, respectively. Fluoxetine didnotaffect theplasma concentration of9-hydroxyrisperidone. Paroxetine lowered theconcentration of9-hydroxyrisperidone byabout 10%.Wheneither concomitant fluoxetine orparoxetine isinitiated ordiscontinued, thephysician should re-evaluate thedosing ofrisperidone. Theeffects ofdiscontinuation
of concomitant fluoxetine orparoxetine therapy onthepharmacokinetics ofrisperidone and9-hydroxyrisperidone havenotbeenstudied.ErythromycinThere werenosignificant interactions between risperidone anderythromycin.7.11 Carbamazepine andOther Enzyme InducersCarbamazepine co-administration decreased thesteady-state plasma concentrations ofrisperidone and9-hydroxyrisperidone byabout 50%.Plasma concentrations ofcarbamazepine didnotappear tobe
affected. Thedoseofrisperidone mayneedtobetitrated accordingly forpatients receiving
carbamazepine, particularly during initiation ordiscontinuation ofcarbamazepine therapy.Coadministration ofother known enzyme inducers (e.g., phenytoin, rifampin, andphenobarbital) with
risperidone maycause similar decreases inthecombined plasma concentrations ofrisperidone and9-hydroxyrisperidone, which could leadtodecreased efficacy ofrisperidone treatment.7.12 Drugs Metabolized byCYP2D6
studies indicate thatrisperidone isarelatively weakinhibitor ofCYP2D6.Therefore, risperidone isnot expected tosubstantially inhibit theclearance ofdrugs thataremetabolized bythisenzymaticpathway. Indruginteraction studies, risperidone didnotsignificantly affect thepharmacokinetics ofdonepezil andgalantamine, which aremetabolized byCYP2D6.Invitro
8 USEINSPECIFIC POPULATIONS
8.1 PregnancyPregnancy Category C.The teratogenic potential ofrisperidone wasstudied inthree Segment IIstudies inSprague-Dawley andWistar rats(0.63 to10mg/kg or0.4to6times themaximum recommended human dose[MRHD] onamg/m basis) andinoneSegment IIstudy inNewZealand rabbits (0.31 to5mg/kg or0.4to6times theMRHD onamg/mbasis). Theincidence ofmalformations wasnotincreased compared tocontrol in
offspring ofratsorrabbits given 0.4to6times theMRHDonamg/mbasis. Inthree reproductive
studies inrats(twoSegment IIIandamultigenerational study), there wasanincrease inpupdeaths during
the first 4daysoflactation atdoses of0.16to5mg/kg or0.1to3times theMRHDonamg/m2 basis. It
is notknown whether these deaths wereduetoadirect effect onthefetuses orpupsortoeffects onthedams. There wasnono-effect doseforincreased ratpupmortality. InoneSegment IIIstudy, there wasan
increase instillborn ratpupsatadoseof2.5mg/kg or1.5times theMRHDonamg/mbasis. Inacross-fostering study inWistar rats, toxic effects onthefetus orpups, asevidenced byadecrease inthenumber oflivepupsandanincrease inthenumber ofdeadpupsatbirth (Day0),andadecrease inbirthweight inpupsofdrug-treated damswereobserved. Inaddition, there wasanincrease indeaths byDay
1 among pupsofdrug-treated dams, regardless ofwhether ornotthepupswerecross-fostered.Risperidone alsoappeared toimpair maternal behavior inthatpupbodyweight gainandsurvival (from
Day 1to4oflactation) werereduced inpupsborntocontrol butreared bydrug-treated dams. These
effects wereallnoted attheonedoseofrisperidone tested, i.e., 5mg/kg or3times theMRHDonamg/m basis. Placental transfer ofrisperidone occurs inratpups. There arenoadequate andwell-controlled studies
in pregnant women. However, there wasonereport ofacaseofagenesis ofthecorpus callosum inan
infant exposed torisperidone .Thecausal relationship torisperidone therapy isunknown. inuteroNon-Teratogenic EffectsNeonates exposed toantipsychotic drugs (including risperidone) during thethird trimester ofpregnancy
are atriskforextrapyramidal and/or withdrawal symptoms following delivery. There havebeenreportsof agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, andfeeding disorder in
these neonates. These complications havevaried inseverity; while insomecases symptoms havebeen
self-limited, inother cases neonates haverequired intensive careunitsupport andprolonged
hospitalization.Risperidone should beusedduring pregnancy onlyifthepotential benefit justifies thepotential riskto
the fetus.8.2 Labor andDeliveryThe effect ofrisperidone onlabor anddelivery inhumans isunknown.8.3 Nursing Mothers
In animal studies, risperidone and9-hydroxyrisperidone areexcreted inmilk. Risperidone and9-hydroxyrisperidone arealsoexcreted inhuman breast milk. Therefore, women receiving risperidone
should notbreast-feed.8.4 Pediatric UseThe efficacy andsafety ofrisperidone inthetreatment ofschizophrenia weredemonstrated in417
adolescents, aged13to17years, intwoshort-term (6and8weeks, respectively) double-blind
controlled trials .Additional safety andefficacy information wasalsoassessed inonelong-term (6-month) open-label extension study in284ofthese adolescent patients withschizophrenia.[seeIndications andUsage (1.1),Adverse Reactions (6.1), andClinical Studies (14.1)]Safety andeffectiveness ofrisperidone inchildren lessthan13years ofagewithschizophrenia havenot beenestablished.The efficacy andsafety ofrisperidone intheshort-term treatment ofacute manic ormixed episodesassociated withBipolar IDisorder in169children andadolescent patients, aged10to17years, weredemonstrated inonedouble-blind, placebo-controlled, 3-week trial .[seeIndications andUsage
(1.2),Adverse Reactions (6.2), andClinical Studies (14.2)]Safety andeffectiveness ofrisperidone inchildren lessthan10years ofagewithbipolar disorder havenot beenestablished.The efficacy andsafety ofrisperidone inthetreatment ofirritability associated withautistic disorderwere established intwo8-week, double-blind, placebo-controlled trials in156children andadolescentpatients, aged5to16years .Additional safety information wasalsoassessed inalong-term study in
patients withautistic disorder, orinshort- andlong-term studies inmorethan1200pediatric patientswith psychiatric disorders other thanautistic disorder, schizophrenia, orbipolar mania whowereofsimilar ageandweight, andwhoreceived similar dosages ofrisperidone aspatients treated for
irritability associated withautistic disorder. [seeIndications andUsage (1.3),Adverse Reactions
(6.3)andClinical Studies (14.4)]The safety andeffectiveness ofrisperidone inpediatric patients lessthan5years ofagewithautisticdisorder havenotbeenestablished.Tardive Dyskinesia
In clinical trials in1885children andadolescents treated withrisperidone, 2(0.1%) patients were
reported tohavetardive dyskinesia, which resolved ondiscontinuation ofrisperidone treatment .[seealsoWarnings andPrecautions (5.4)]Weight Gain
In along-term, open-label extension study inadolescent patients withschizophrenia, weight increasewas reported asatreatment-emergent adverse event in14%ofpatients. In103adolescent patients with
schizophrenia, ameanincrease of9.0kgwasobserved after 8months ofrisperidone treatment. Themajority ofthatincrease wasobserved within thefirst 6months. Theaverage percentiles atbaseline and
8 months, respectively, were56and72forweight, 55and58forheight, and51and71forbodymass
index.In long-term, open-label trials (studies inpatients withautistic disorder orother psychiatric disorders),a meanincrease of7.5kgafter 12months ofrisperidone treatment wasobserved, which washigher than
the expected normal weight gain(approximately 3to3.5kgperyearadjusted forage,based onCenters
for Disease Control andPrevention normative data). Themajority ofthatincrease occurred within the
first 6months ofexposure torisperidone. Theaverage percentiles atbaseline and12months,respectively, were49and60forweight, 48and53forheight, and50and62forbodymassindex.In one3-week, placebo-controlled trial inchildren andadolescent patients withacute manic ormixed
episodes ofbipolar Idisorder, increases inbodyweight werehigher intherisperidone groups thantheplacebo group, butnotdoserelated (1.90 kgintherisperidone 0.5to2.5mggroup, 1.44kginthe
risperidone 3to6mggroup, and0.65kgintheplacebo group). Asimilar trend wasobserved inthemean change frombaseline inbodymassindex.When treating pediatric patients withrisperidone foranyindication, weight gainshould beassessed
against thatexpected withnormal growth. [SeealsoAdverse Reactions (6.7)]SomnolenceSomnolence wasfrequently observed inplacebo-controlled clinical trials ofpediatric patients with
autistic disorder. Mostcases weremildormoderate inseverity. These events weremostoften ofearly
onset withpeakincidence occurring during thefirst twoweeks oftreatment, andtransient withamedian
duration of16days. Somnolence wasthemostcommonly observed adverse event intheclinical trial ofbipolar disorder inchildren andadolescents, aswellasintheschizophrenia trials inadolescents. Aswas seenintheautistic disorder trials, these events weremostoften ofearly onset andtransient in
duration. Patients experiencing persistent somnolence maybenefit fromachange indosing regimen .[See alsoAdverse Reactions (6.1,6.2,6.3)][seeDosage andAdministration (2.1,2.2,2.3)]Hyperprolactinemia, Growth, andSexual MaturationRisperidone hasbeenshown toelevate prolactin levels inchildren andadolescents aswellasinadults .In double-blind, placebo-controlled studies ofupto8weeks duration inchildren andadolescents (aged
5 to17years) withautistic disorder orpsychiatric disorders other thanautistic disorder, schizophrenia,or bipolar mania, 49%ofpatients whoreceived risperidone hadelevated prolactin levels compared to
2% ofpatients whoreceived placebo. Similarly, inplacebo-controlled trials inchildren andadolescents
(aged 10to17years) withbipolar disorder, oradolescents (aged 13to17years) withschizophrenia, 82
to 87%ofpatients whoreceived risperidone hadelevated levels ofprolactin compared to3to7%ofpatients onplacebo. Increases weredose-dependent andgenerally greater infemales thaninmalesacross indications. [seeWarnings andPrecautions (5.6)]
In clinical trials in1885children andadolescents, galactorrhea wasreported in0.8%ofrisperidone-treated patients andgynecomastia wasreported in2.3%ofrisperidone-treated patients.The long-term effects ofrisperidone ongrowth andsexual maturation havenotbeenfully evaluated.8.5 Geriatric UseClinical studies ofrisperidone inthetreatment ofschizophrenia didnotinclude sufficient numbers ofpatients aged65andovertodetermine whether ornottheyrespond differently thanyounger patients.Other reported clinical experience hasnotidentified differences inresponses between elderly and
younger patients. Ingeneral, alower starting doseisrecommended foranelderly patient, reflecting adecreased pharmacokinetic clearance intheelderly, aswellasagreater frequency ofdecreased
hepatic, renal, orcardiac function, andofconcomitant disease orother drugtherapy .While elderly
patients exhibit agreater tendency toorthostatic hypotension, itsriskintheelderly maybeminimized by
limiting theinitial doseto0.5mgtwice daily followed bycareful titration .Monitoring oforthostaticvital signs should beconsidered inpatients forwhomthisisofconcern. [seeClinical Pharmacology
(12.3)andDosage andAdministration (2.4,2.5)][seeWarnings andPrecautions (5.7)]This drugissubstantially excreted bythekidneys, andtheriskoftoxic reactions tothisdrugmaybegreater inpatients withimpaired renal function. Because elderly patients aremorelikely tohavedecreased renal function, careshould betaken indoseselection, anditmaybeuseful tomonitor renalfunction .[seeDosage andAdministration (2.4)]Concomitant usewithFurosemide inElderly Patients withDementia-Related Psychosis
In twooffourplacebo-controlled trials inelderly patients withdementia-related psychosis, ahigher
incidence ofmortality wasobserved inpatients treated withfurosemide plusrisperidone when
compared topatients treated withrisperidone alone orwithplacebo plusfurosemide. Nopathologicalmechanism hasbeenidentified toexplain thisfinding, andnoconsistent pattern forcause ofdeath wasobserved. Anincrease ofmortality inelderly patients withdementia-related psychosis wasseenwith
the useofrisperidone regardless ofconcomitant usewithfurosemide. Risperidone isnotapproved for
the treatment ofpatients withdementia-related psychosis. [SeeBoxed WarningandWarnings andPrecautions (5.1)]9 DRUGABUSE ANDDEPENDENCE
9.1 Controlled SubstanceRisperidone isnotacontrolled substance.9.2 AbuseRisperidone hasnotbeensystematically studied inanimals orhumans foritspotential forabuse. While
the clinical trials didnotreveal anytendency foranydrug-seeking behavior, these observations werenot systematic anditisnotpossible topredict onthebasis ofthislimited experience theextent towhich
a CNS-active drugwillbemisused, diverted, and/or abused oncemarketed. Consequently, patients
should beevaluated carefully forahistory ofdrugabuse, andsuchpatients should beobserved closely
for signs ofrisperidone misuse orabuse (e.g., development oftolerance, increases indose, drug-seeking behavior).9.3 DependenceRisperidone hasnotbeensystematically studied inanimals orhumans foritspotential fortolerance orphysical dependence.10 OVERDOSAGE
10.1 Human ExperiencePremarketing experience included eight reports ofacute risperidone overdosage withestimated doses
ranging from20to300mgandnofatalities. Ingeneral, reported signs andsymptoms werethose
resulting fromanexaggeration ofthedrug's known pharmacological effects, i.e., drowsiness and
sedation, tachycardia andhypotension, andextrapyramidal symptoms. Onecase, involving anestimated
overdose of240mg,wasassociated withhyponatremia, hypokalemia, prolonged QT,andwidenedQRS. Another case, involving anestimated overdose of36mg,wasassociated withaseizure.Postmarketing experience includes reports ofacute risperidone overdosage, withestimated doses ofup
to 360mg.Ingeneral, themostfrequently reported signs andsymptoms arethose resulting froman
exaggeration ofthedrug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia,hypotension, andextrapyramidal symptoms. Other adverse reactions reported since market introduction
related torisperidone overdose include prolonged QTinterval andconvulsions. Torsade depointes hasbeen reported inassociation withcombined overdose ofrisperidone andparoxetine.10.2 Management ofOverdosage
In caseofacute overdosage, establish andmaintain anairway andensure adequate oxygenation and
ventilation. Gastric lavage (after intubation, ifpatient isunconscious) andadministration ofactivated
charcoal together withalaxative should beconsidered.The possibility ofobtundation, seizures, ordystonic reaction oftheheadandneckfollowing overdosemay create ariskofaspiration withinduced emesis. Cardiovascular monitoring should commence
immediately andshould include continuous electrocardiographic monitoring todetect possible
arrhythmias. Ifantiarrhythmic therapy isadministered, disopyramide, procainamide, andquinidine carry a
theoretical hazard ofQT-prolonging effects thatmight beadditive tothose ofrisperidone. Similarly, it
is reasonable toexpect thatthealpha-blocking properties ofbretylium might beadditive tothose of
risperidone, resulting inproblematic hypotension.There isnospecific antidote torisperidone. Therefore, appropriate supportive measures should be
instituted. Thepossibility ofmultiple druginvolvement should beconsidered. Hypotension and
circulatory collapse should betreated withappropriate measures, suchasintravenous fluids and/orsympathomimetic agents (epinephrine anddopamine should notbeused, since betastimulation mayworsen hypotension inthesetting ofrisperidone-induced alpha blockade). Incases ofsevere
extrapyramidal symptoms, anticholinergic medication should beadministered. Close medicalsupervision andmonitoring should continue until thepatient recovers.11 DESCRIPTION
Risperidone oralsolution, USPcontains risperidone, apsychotropic agent belonging tothechemicalclass ofbenzisoxazole derivatives. Thechemical designation is3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one. Itsmolecular
formula isCHFNOanditsmolecular weight is410.49. Thestructural formula is:Risperidone isawhite toslightly beige powder. Itispractically insoluble inwater, freely soluble inmethylene chloride, andsoluble inmethanol and0.1NHCl.Risperidone oralsolution, USPisavailable asa1mg/mL oralsolution. Risperidone oralsolution, USP
contains thefollowing inactive ingredients: benzoic acidandpurified water.12 CLINICAL PHARMACOLOGY
12.1 Mechanism ofActionThe mechanism ofaction ofrisperidone, aswithother drugs usedtotreat schizophrenia, isunknown.However, ithasbeenproposed thatthedrug's therapeutic activity inschizophrenia ismediated through
a combination ofdopamine Type2(D)andserotonin Type2(5HT)receptor antagonism. Risperidone isaselective monoaminergic antagonist withhighaffinity (Kiof0.12to7.3nM)forthe
serotonin Type2(5HT),dopamine Type2(D),α1andα2adrenergic, andHhistaminergic receptors.Risperidone actsasanantagonist atother receptors, butwithlower potency. Risperidone haslowtomoderate affinity (Kiof47to253nM)fortheserotonin 5HT,5HT,and5HTreceptors, weakaffinity
(Ki of620to800nM)forthedopamine Dandhaloperidol-sensitive sigma site, andnoaffinity (when
tested atconcentrations >10M)forcholinergic muscarinic orβandβadrenergic receptors. 12.2 PharmacodynamicsThe clinical effect fromrisperidone results fromthecombined concentrations ofrisperidone anditsmajor metabolite, 9-hydroxyrisperidone .Antagonism atreceptors other thanDand5HTmayexplain
some oftheother effects ofrisperidone. [seeClinical Pharmacology (12.3)][seeClinical Pharmacology
(12.1)]12.3 PharmacokineticsAbsorptionRisperidone iswellabsorbed. Theabsolute oralbioavailability ofrisperidone is70%(CV=25%). The
relative oralbioavailability ofrisperidone fromatablet is94%(CV=10%) whencompared toa
solution.Pharmacokinetic studies showed thatRisperidone Orally Disintegrating Tablets andRisperidone OralSolution arebioequivalent toRisperidone Tablets.Plasma concentrations ofrisperidone, itsmajor metabolite, 9-hydroxyrisperidone, andrisperidone plus9-hydroxyrisperidone aredoseproportional overthedosing range of1to16mgdaily (0.5to8mg
twice daily). Following oraladministration ofsolution ortablet, meanpeakplasma concentrations of
risperidone occurred atabout 1hour. Peakconcentrations of9-hydroxyrisperidone occurred atabout 3
hours inextensive metabolizers, and17hours inpoormetabolizers. Steady-state concentrations of
risperidone arereached in1dayinextensive metabolizers andwould beexpected toreach steady-state
in about 5daysinpoormetabolizers. Steady-state concentrations of9-hydroxyrisperidone arereached
in 5to6days(measured inextensive metabolizers).Food EffectFood doesnotaffect either therateorextent ofabsorption ofrisperidone. Thus, risperidone canbegiven withorwithout meals.DistributionRisperidone israpidly distributed. Thevolume ofdistribution is1to2L/kg. Inplasma, risperidone isbound toalbumin andα1-acid glycoprotein. Theplasma protein binding ofrisperidone is90%,andthatof itsmajor metabolite, 9-hydroxyrisperidone, is77%.Neither risperidone nor9-hydroxyrisperidonedisplaces eachother fromplasma binding sites. Hightherapeutic concentrations ofsulfamethazine (100mcg/mL), warfarin (10mcg/mL), andcarbamazepine (10mcg/mL) caused onlyaslight increase inthe
free fraction ofrisperidone at10ng/mL and9-hydroxyrisperidone at50ng/mL, changes ofunknown
clinical significance.Metabolism andDrugInteractionsRisperidone isextensively metabolized intheliver. Themainmetabolic pathway isthrough
hydroxylation ofrisperidone to9-hydroxyrisperidone bytheenzyme, CYP2D6.Aminor metabolicpathway isthrough -dealkylation. Themainmetabolite, 9-hydroxyrisperidone, hassimilarpharmacological activity asrisperidone. Consequently, theclinical effect ofthedrugresults fromthe
combined concentrations ofrisperidone plus9-hydroxyrisperidone. N
CYP 2D6,alsocalled debrisoquin hydroxylase, istheenzyme responsible formetabolism ofmany
neuroleptics, antidepressants, antiarrhythmics, andother drugs. CYP2D6issubject togeneticpolymorphism (about 6%-8% ofCaucasians, andaverylowpercentage ofAsians, havelittle orno
activity andare“poor metabolizers”) andtoinhibition byavariety ofsubstrates andsomenon-substrates, notably quinidine. Extensive CYP2D6metabolizers convert risperidone rapidly into9-hydroxyrisperidone, whereas poorCYP2D6metabolizers convert itmuchmoreslowly. Although
extensive metabolizers havelower risperidone andhigher 9-hydroxyrisperidone concentrations than
poor metabolizers, thepharmacokinetics ofrisperidone and9-hydroxyrisperidone combined, aftersingle andmultiple doses, aresimilar inextensive andpoormetabolizers.Risperidone could besubject totwokinds ofdrug-drug interactions. First, inhibitors ofCYP2D6
interfere withconversion ofrisperidone to9-hydroxyrisperidone .Thisoccurs withquinidine, giving
essentially allrecipients arisperidone pharmacokinetic profile typical ofpoormetabolizers. The
therapeutic benefits andadverse effects ofrisperidone inpatients receiving quinidine havenotbeen
evaluated, butobservations inamodest number (n�70) ofpoormetabolizers given risperidone donotsuggest important differences between poorandextensive metabolizers. Second, co-administration ofknown enzyme inducers (e.g., carbamazepine, phenytoin, rifampin, andphenobarbital) withrisperidonemay cause adecrease inthecombined plasma concentrations ofrisperidone and9-hydroxyrisperidone .It would alsobepossible forrisperidone tointerfere withmetabolism ofother drugs metabolized byCYP 2D6.Relatively weakbinding ofrisperidone totheenzyme suggests thisisunlikely .[seeDrug
Interactions (7.12)][seeDrug Interactions (7.11)][seeDrug Interactions 7.12)]ExcretionRisperidone anditsmetabolites areeliminated viatheurine and,toamuchlesser extent, viathefeces.As illustrated byamassbalance study ofasingle 1mgoraldoseof14C-risperidone administered as
solution tothree healthy malevolunteers, total recovery ofradioactivity at1weekwas84%,including
70% intheurine and14%inthefeces.The apparent half-life ofrisperidone was3hours (CV=30%) inextensive metabolizers and20hours
(CV=40%) inpoormetabolizers. Theapparent half-life of9-hydroxyrisperidone wasabout 21hours
(CV=20%) inextensive metabolizers and30hours (CV=25%) inpoormetabolizers. Thepharmacokinetics ofrisperidone and9-hydroxyrisperidone combined, after single andmultiple doses,were similar inextensive andpoormetabolizers, withanoverall meanelimination half-life ofabout 20
hours.Renal ImpairmentIn patients withmoderate tosevere renal disease, clearance ofthesumofrisperidone anditsactivemetabolite decreased by60%compared toyoung healthy subjects. Risperidone doses should be
reduced inpatients withrenal disease [seeDosage andAdministration (2.4)andWarnings andPrecautions
(5.17)].Hepatic ImpairmentWhile thepharmacokinetics ofrisperidone insubjects withliver disease werecomparable tothose in
young healthy subjects, themeanfreefraction ofrisperidone inplasma wasincreased byabout 35%
because ofthediminished concentration ofbothalbumin andα1-acid glycoprotein. Risperidone doses
should bereduced inpatients withliver disease .[seeDosage andAdministration (2.4)andWarnings andPrecautions (5.17)]Elderly
In healthy elderly subjects, renal clearance ofbothrisperidone and9-hydroxyrisperidone wasdecreased, andelimination half-lives wereprolonged compared toyoung healthy subjects. Dosing
should bemodified accordingly intheelderly patients .[seeDosage andAdministration (2.4)]PediatricThe pharmacokinetics ofrisperidone and9-hydroxyrisperidone inchildren weresimilar tothose in
adults after correcting forthedifference inbodyweight.Race andGender EffectsNo specific pharmacokinetic study wasconducted toinvestigate raceandgender effects, butapopulation pharmacokinetic analysis didnotidentify important differences inthedisposition of
risperidone duetogender (whether corrected forbodyweight ornot)orrace.13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment ofFertilityCarcinogenesisCarcinogenicity studies wereconducted inSwiss albino miceandWistar rats. Risperidone wasadministered inthedietatdoses of0.63mg/kg, 2.5mg/kg, and10mg/kg for18months tomiceandfor25 months torats. These doses areequivalent to2.4,9.4,and37.5times themaximum recommended
human dose(MRHD) forschizophrenia (16mg/day) onamg/kg basis or0.2,0.75, and3times theMRHD (mice) or0.4,1.5,and6times theMRHD(rats) onamg/mbasis. Amaximum tolerated dosewasnot achieved inmalemice. There werestatistically significant increases inpituitary gland adenomas,endocrine pancreas adenomas, andmammary gland adenocarcinomas. Thefollowing table summarizes
the multiples ofthehuman doseonamg/m(mg/kg) basis atwhich these tumors occurred. Multiples ofMaximumHuman Doseinmg/mmg/kg)Tumor TypeSpeciesSexLowest EffectLevelHighest No-EffectLevelPituitary adenomasmousefemale0.75 (9.4)0.2 (2.4)Endocrine pancreasadenomas
ratmale1.5 (9.4)0.4 (2.4)Mammary gland
adenocarcinomasmousefemale0.2 (2.4)none
ratfemale0.4 (2.4)none
ratmale6.0 (37.5)1.5 (9.4)Mammary gland neoplasm,Totalratmale1.5 (9.4)0.4 (2.4)Antipsychotic drugs havebeenshown tochronically elevate prolactin levels inrodents. Serum prolactin
levels werenotmeasured during therisperidone carcinogenicity studies; however, measurementsduring subchronic toxicity studies showed thatrisperidone elevated serum prolactin levels 5to6fold
in miceandratsatthesamedoses usedinthecarcinogenicity studies. Anincrease inmammary, pituitary,and endocrine pancreas neoplasms hasbeenfound inrodents after chronic administration ofotherantipsychotic drugs andisconsidered tobeprolactin-mediated. Therelevance forhuman riskofthe
findings ofprolactin-mediated endocrine tumors inrodents isunknown .[seeWarnings andPrecautions
(5.6)]MutagenesisNo evidence ofmutagenic potential forrisperidone wasfound intheAmesreverse mutation test, mouse
lymphoma assay, rathepatocyte DNA-repair assay, micronucleus testinmice, thesex-linked recessive
lethal testin,orthechromosomal aberration testinhuman lymphocytes orChinese hamster cells. in
vitroin vivoDrosophila
Impairment ofFertilityRisperidone (0.16 to5mg/kg) wasshown toimpair mating, butnotfertility, inWistar ratsinthree
reproductive studies (twoSegment Iandamultigenerational study) atdoses 0.1to3times themaximum
recommended human dose(MRHD) onamg/mbasis. Theeffect appeared tobeinfemales, since
impaired mating behavior wasnotnoted intheSegment Istudy inwhich males onlyweretreated. Ina
subchronic study inBeagle dogsinwhich risperidone wasadministered atdoses of0.31to5mg/kg,sperm motility andconcentration weredecreased atdoses 0.6to10times theMRHDonamg/mbasis.Dose-related decreases werealsonoted inserum testosterone atthesamedoses. Serum testosterone
and sperm parameters partially recovered, butremained decreased after treatment wasdiscontinued. No
no-effect doses werenoted ineither ratordog.14 CLINICAL STUDIES
14.1 SchizophreniaAdultsShort-Term EfficacyThe efficacy ofrisperidone inthetreatment ofschizophrenia wasestablished infourshort-term (4-to
8-week) controlled trials ofpsychotic inpatients whometDSM-III-R criteria forschizophrenia.Several instruments wereusedforassessing psychiatric signs andsymptoms inthese studies, among
them theBrief Psychiatric Rating Scale (BPRS), amulti-item inventory ofgeneral psychopathology
traditionally usedtoevaluate theeffects ofdrugtreatment inschizophrenia. TheBPRSpsychosiscluster (conceptual disorganization, hallucinatory behavior, suspiciousness, andunusual thoughtcontent) isconsidered aparticularly useful subset forassessing actively psychotic schizophrenicpatients. Asecond traditional assessment, theClinical Global Impression (CGI), reflects theimpression
of askilled observer, fully familiar withthemanifestations ofschizophrenia, about theoverall clinicalstate ofthepatient. Inaddition, thePositive andNegative Syndrome Scale (PANSS) andtheScale forAssessing Negative Symptoms (SANS) wereemployed.The results ofthetrials follow:Long-Term Efficacy
In alonger-term trial, 365adult outpatients predominantly meeting DSM-IV criteria forschizophrenia
and whohadbeenclinically stable foratleast 4weeks onanantipsychotic medication wererandomized
to risperidone (2to8mg/day) ortoanactive comparator, for1to2years ofobservation forrelapse.Patients receiving risperidone experienced asignificantly longer timetorelapse overthistimeperiod
compared tothose receiving theactive comparator.PediatricsThe efficacy ofrisperidone inthetreatment ofschizophrenia inadolescents aged13to17years wasdemonstrated intwoshort-term (6and8weeks), double-blind controlled trials. Allpatients metDSM-IV
diagnostic criteria forschizophrenia andwereexperiencing anacute episode attimeofenrollment. In
the first trial (study #1),patients wererandomized intooneofthree treatment groups: risperidone 1to3mg/day (n=55,meanmodal dose=2.6mg),risperidone 4to6mg/day (n=51,meanmodal dose=5.3mg), orplacebo (n=54).Inthesecond trial (study #2),patients wererandomized toeither risperidone0.15 to0.6mg/day (n=132,meanmodal dose=0.5mg)orrisperidone 1.5to6mg/day (n=125,meanmodal dose=4mg).Inallcases, study medication wasinitiated at0.5mg/day (with theexception ofthe0.15 to0.6mg/day group instudy #2,where theinitial dosewas0.05mg/day) andtitrated tothetargetdosage range byapproximately Day7.Subsequently, dosage wasincreased tothemaximum tolerated
dose within thetarget doserange byDay14.Theprimary efficacy variable inallstudies wasthemean
change frombaseline intotal PANSS score.Results ofthestudies demonstrated efficacy ofrisperidone inalldosegroups from1-6mg/day
compared toplacebo, asmeasured bysignificant reduction oftotal PANSS score. Theefficacy ontheprimary parameter inthe1to3mg/day group wascomparable tothe4to6mg/day group instudy #1,and
similar totheefficacy demonstrated inthe1.5to6mg/day group instudy #2.Instudy #2,theefficacy in
the 1.5to6mg/day group wasstatistically significantly greater thanthatinthe0.15to0.6mg/day group.Doses higher than3mg/day didnotreveal anytrend towards greater efficacy.14.2 Bipolar Mania -MonotherapyAdultsThe efficacy ofrisperidone inthetreatment ofacute manic ormixed episodes wasestablished intwo
short-term (3-week) placebo-controlled trials inpatients whomettheDSM-IV criteria forBipolar IDisorder withmanic ormixed episodes. These trials included patients withorwithout psychotic
features.The primary rating instrument usedforassessing manic symptoms inthese trials wastheYoung ManiaRating Scale (YMRS), an11-item clinician-rated scale traditionally usedtoassess thedegree ofmanic
symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased
activity, sexual interest, language/thought disorder, thought content, appearance, andinsight) inarange
from 0(nomanic features) to60(maximum score). Theprimary outcome inthese trials waschange
from baseline intheYMRStotal score. Theresults ofthetrials follow:PediatricsThe efficacy ofrisperidone inthetreatment ofmania inchildren oradolescents withBipolar Idisorderwas demonstrated ina3-week, randomized, double-blind, placebo-controlled, multicenter trial including
patients ranging inagesfrom10to17years whowereexperiencing amanic ormixed episode ofbipolar Idisorder. Patients wererandomized intooneofthree treatment groups: risperidone 0.5to2.5mg/day (n=50,meanmodal dose=1.9mg),risperidone 3to6mg/day (n=61,meanmodal dose=4.7mg), orplacebo (n=58).Inallcases, study medication wasinitiated at0.5mg/day andtitrated tothe
target dosage range byDay7,withfurther increases indosage tothemaximum tolerated dosewithin the
targeted doserange byDay10.Theprimary rating instrument usedforassessing efficacy inthisstudywas themeanchange frombaseline inthetotal YMRSscore.Results ofthisstudy demonstrated efficacy ofrisperidone inbothdosegroups compared withplacebo,as measured bysignificant reduction oftotal YMRSscore. Theefficacy ontheprimary parameter inthe3 to6mg/day dosegroup wascomparable tothe0.5to2.5mg/day dosegroup. Doses higher than2.5mg/day didnotreveal anytrend towards greater efficacy.14.3 Bipolar Mania –Combination TherapyThe efficacy ofrisperidone withconcomitant lithium orvalproate inthetreatment ofacute manic ormixed episodes wasestablished inonecontrolled trial inadult patients whomettheDSM-IV criteria forBipolar IDisorder. Thistrial included patients withorwithout psychotic features andwithorwithout a
rapid-cycling course.14.4 Irritability Associated withAutistic DisorderShort-Term EfficacyThe efficacy ofrisperidone inthetreatment ofirritability associated withautistic disorder wasestablished intwo8-week, placebo-controlled trials inchildren andadolescents (aged 5to16years)who mettheDSM-IV criteria forautistic disorder. Over90%ofthese subjects wereunder 12years ofage andmostweighed over20kg(16-104.3 kg).Efficacy wasevaluated using twoassessment scales: theAberrant Behavior Checklist (ABC) andtheClinical Global Impression -Change (CGI-C) scale. Theprimary outcome measure inbothtrials was
the change frombaseline toendpoint intheIrritability subscale oftheABC(ABC-I). TheABC-Isubscale measured theemotional andbehavioral symptoms ofautism, including aggression towardsothers, deliberate self-injuriousness, temper tantrums, andquickly changing moods. TheCGI-C rating atendpoint wasaco-primary outcome measure inoneofthestudies.The results ofthese trials areasfollows:Long-Term EfficacyFollowing completion ofthefirst 8-week double-blind study, 63patients entered anopen-label study
extension where theyweretreated withrisperidone for4or6months (depending onwhether they
received risperidone orplacebo inthedouble-blind study). During thisopen-label treatment period,patients weremaintained onameanmodal doseofrisperidone of1.8to2.1mg/day (equivalent to0.05to
0.07 mg/kg/day).Patients whomaintained their positive response torisperidone (response wasdefined as≥25%
improvement ontheABC-I subscale andaCGI-C rating of‘much improved’ or‘very muchimproved’)during the4to6month open-label treatment phase forabout 140days, onaverage, wererandomized to
receive risperidone orplacebo during an8-week, double-blind withdrawal study (n=39 ofthe63
patients). Apre-planned interim analysis ofdatafrompatients whocompleted thewithdrawal study
(n=32), undertaken byanindependent DataSafety Monitoring Board, demonstrated asignificantly lower
relapse rateintherisperidone group compared withtheplacebo group. Based ontheinterim analysis
results, thestudy wasterminated duetodemonstration ofastatistically significant effect onrelapseprevention. Relapse wasdefined as≥25%worsening onthemostrecent assessment oftheABC-Isubscale (inrelation tobaseline oftherandomized withdrawal phase).17 PATIENT COUNSELING INFORMATION
Physicians areadvised todiscuss thefollowing issues withpatients forwhomtheyprescribe
risperidone:17.1 Orthostatic Hypotension
Patients should beadvised oftheriskoforthostatic hypotension, especially during theperiod ofinitialdose titration .[seeWarnings andPrecautions (5.7)]17.2 Interference withCognitive andMotor PerformanceSince risperidone hasthepotential toimpair judgment, thinking, ormotor skills, patients should be
cautioned about operating hazardous machinery, including automobiles, until theyarereasonably certain
that risperidone therapy doesnotaffect themadversely .[seeWarnings andPrecautions (5.9)]17.3 PregnancyPatients should beadvised tonotify their physician iftheybecome pregnant orintend tobecomepregnant during therapy .[seeUse inSpecific Populations (8.1)]17.4 NursingPatients should beadvised nottobreast-feed aninfant iftheyaretaking risperidone .[seeUse inSpecificPopulations (8.3)]17.5 Concomitant Medication
Patients should beadvised toinform their physicians iftheyaretaking, orplantotake, anyprescription
or over-the-counter drugs, since there isapotential forinteractions .[seeDrug Interactions (7)]17.6 AlcoholPatients should beadvised toavoid alcohol while taking risperidone .[seeDrug Interactions (7.1)]Rx OnlyManufactured by:Amneal PharmaceuticalsBranchburg, NJ08876Distributed by:Amneal PharmaceuticalsGlasgow, KY42141Rev. 04-2011Risperidone OralSolution, USP
PHARMACIST:TEAR ATPERFORATION ANDGIVETOPATIENTUSING YOURRISPERIDONE DISPENSING-PIPETTE ANDBOTTLENDC 65162-673-84 30mLRisperidone OralSolution, USP
1mg/mL
Each 1mLcontains: 1mgofrisperidone inanaqueous solution.Use thisproduct asindicated below, unless directed otherwise byyourPhysician.IMPORTANT: Please readthese instructions before using risperidone oralsolution.1. Pushtheplastic screw-cap onthebottle downwhile turning itcounter-clockwise. Remove theunscrewed cap(seeFigure 1).2. Insert thedispensing-pipette fully intothebottle (seeFigure 2).3. While holding theouter barrel ofthepipette, pulltheplunger uptothelevel (seemarkings onside) thatequals thedosage prescribed byyourphysician (seeFigure 3).4. Holding theouter barrel ofthepipette, remove theentire pipette fromthebottle, being careful nottodepress theplunger prematurely (seeFigure 4).5. Empty theentire contents ofthepipette into3to4ounces (100mL) ofabeverage bypushing theplunger downinside thepipette barrel. Stirthemixture thoroughly before consuming. Risperidone OralSolution iscompatible withwater, coffee, orange juice, orlow-fat milk: ITISNOTCOMPATIBLE withcolaortea.6. Replace theplastic caponthebottle byscrewing itclockwise; rinse theempty dispensing-pipette withwater.DOSAGE: Forinformation about theuseofrisperidone, please seeaccompanying Package Insert.STORAGE: Store bottle at20°to25°C(68°to77°F) [SeeUSPControlled RoomTemperature]. Keep
away fromchildren; avoid freezing andprotect fromlight.Manufactured by:Amneal PharmaceuticalsBranchburg, NJ08876Distributed by:Amneal PharmaceuticalsGlasgow, KY42141Rev. 04-2011RISPERIDONE SOLUTIONRISPERIDONE risperidone solutionProduct Information
Product TypeHUMAN PRESCRIPTION DRUGItem Code(Source)NDC:17856-0380(NDC:65162-673)Route ofAdministrationORALActive Ingredient/Active Moiety
Ingredient NameBasis ofStrengthStrengthRISPERIDONE(UNII: L6UH7ZF8HC) (RISPERIDONE -UNII:L6UH7ZF8HC)RISPERIDONE1 mgin1mL
Inactive Ingredients
Ingredient NameStrengthBENZOIC ACID (UNII: 8SKN0B0MIM) WATER (UNII: 059QF0KO0R) Packaging
#Item CodePackage DescriptionMarketing Start DateMarketing EndDate
1NDC:17856-0380-11 mLin1SYRINGE
2NDC:17856-0380-22 mLin1SYRINGEMarketing InformationMarketing CategoryApplication Number orMonograph CitationMarketing Start DateMarketing EndDateANDAANDA09138405/31/2011Labeler -Atlantic Biologicals Corps (047437707)Registrant -Atlantic Biologicals Corps (047437707)EstablishmentNameAddressID/FEIBusiness OperationsAtlantic Biologicals Corps047437707RELABEL, REPACK

Sections orsubsections omitted fromthefullprescribing information arenotlisted.
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Increased mortality inelderly patients withdementia-related psychosis [seeand]BoxedWarningWarnings andPrecautions (5.1)Cerebrovascular adverse events, including stroke, inelderly patients withdementia-related
psychosis [see]Warnings andPrecautions (5.2)Neuroleptic malignant syndrome [see]Warnings andPrecautions (5.3)Tardive dyskinesia [see]Warnings andPrecautions (5.4)Hyperglycemia anddiabetes mellitus [see]Warnings andPrecautions (5.5)Hyperprolactinemia [see]Warnings andPrecautions (5.6)Orthostatic hypotension [see]Warnings andPrecautions (5.7)Leukopenia, neutropenia, andagranulocytosis [see]Warnings andPrecautions (5.8)Potential forcognitive andmotor impairment [see]Warnings andPrecautions (5.9)Seizures [see]Warnings andPrecautions (5.10)Dysphagia [see]Warnings andPrecautions (5.11)Priapism [see]Warnings andPrecautions (5.12)Thrombotic Thrombocytopenic Purpura (TTP) [see]Warnings andPrecautions (5.13)Disruption ofbodytemperature regulation [see]Warnings andPrecautions (5.14)Antiemetic effect [see]Warnings andPrecautions (5.15)Suicide [see]Warnings andPrecautions (5.16)
Increased sensitivity inpatients withParkinson’s disease orthose withdementia withLewybodies
[see]Warnings andPrecautions (5.17)Diseases orconditions thatcould affect metabolism orhemodynamic responses [see]Warningsand Precautions (5.17)
* Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, parkinsonism,cogwheel rigidity, akinesia, bradykinesia, hypokinesia, masked facies, muscle rigidity, andParkinson’s disease. Akathisia includes akathisia andrestlessness. Dystonia includes dystonia,muscle spasms, muscle contractions involuntary, muscle contracture, oculogyration, tongueparalysis. Tremor includes tremor andparkinsonian resttremor. Dyskinesia includes dyskinesia,muscle twitching, chorea, andchoreoathetosis.* Parkinsonism includes extrapyramidal disorder, muscle rigidity, musculoskeletal stiffness, and
hypokinesia. Akathisia includes akathisia andrestlessness. Dystonia includes dystonia and
oculogyration.
* Parkinsonism includes extrapyramidal disorder, parkinsonism, musculoskeletal stiffness,hypokinesia, muscle rigidity, muscle tightness, bradykinesia, cogwheel rigidity. Akathisia
includes akathisia andrestlessness. Tremor includes tremor andparkinsonian resttremor. Dystonia
includes dystonia, muscle spasms, oculogyration, torticollis. Dyskinesia includes muscle
twitching anddyskinesia.
* Parkinsonism includes extrapyramidal disorder, hypokinesia andbradykinesia. Akathisia includeshyperkinesia andakathisia.
* Parkinsonism includes musculoskeletal stiffness, extrapyramidal disorder, bradykinesia, and
nuchal rigidity. Dystonia includes dystonia, laryngospasm, andmuscle spasms. Akathisia includes
restlessness andakathisia.
* Parkinsonism includes musculoskeletal stiffness, extrapyramidal disorder, muscle rigidity,cogwheel rigidity, andmuscle tightness.
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(1) Ina6-week, placebo-controlled trial (n=160) involving titration ofrisperidone indoses upto
10 mg/day (twice-daily schedule), risperidone wasgenerally superior toplacebo ontheBPRS
total score, ontheBPRSpsychosis cluster, andmarginally superior toplacebo ontheSANS.(2) Inan8-week, placebo-controlled trial (n=513) involving 4fixed doses ofrisperidone (2mg/day, 6mg/day, 10mg/day, and16mg/day, onatwice-daily schedule), all4risperidone groupswere generally superior toplacebo ontheBPRStotal score, BPRSpsychosis cluster, andCGIseverity score; the3highest risperidone dosegroups weregenerally superior toplacebo onthePANSS negative subscale. Themostconsistently positive responses onallmeasures wereseen
for the6mgdosegroup, andthere wasnosuggestion ofincreased benefit fromlarger doses.(3) Inan8-week, dosecomparison trial (n=1356) involving 5fixed doses ofrisperidone (1mg/day, 4mg/day, 8mg/day, 12mg/day, and16mg/day, onatwice-daily schedule), thefourhighest risperidone dosegroups weregenerally superior tothe1mgrisperidone dosegroup onBPRS total score, BPRSpsychosis cluster, andCGIseverity score. Noneofthedosegroupswere superior tothe1mggroup onthePANSS negative subscale. Themostconsistently positive
responses wereseenforthe4mgdosegroup.(4) Ina4-week, placebo-controlled dosecomparison trial (n=246) involving 2fixed doses of
risperidone (4and8mg/day onaonce-daily schedule), bothrisperidone dosegroups weregenerally superior toplacebo onseveral PANSS measures, including aresponse measure (>20%
reduction inPANSS total score), PANSS total score, andtheBPRSpsychosis cluster (derived
from PANSS). Theresults weregenerally stronger forthe8mgthanforthe4mgdosegroup.
(1) Inone3-week placebo-controlled trial (n=246), limited topatients withmanic episodes, which
involved adoserange ofrisperidone 1to6mg/day, oncedaily, starting at3mg/day (mean modaldose was4.1mg/day), risperidone wassuperior toplacebo inthereduction ofYMRStotal score.(2) Inanother 3-week placebo-controlled trial (n=286), which involved adoserange of1to6mg/day, oncedaily, starting at3mg/day (mean modal dosewas5.6mg/day), risperidone was
superior toplacebo inthereduction ofYMRStotal score.(1) Inthis3-week placebo-controlled combination trial, 148in-oroutpatients onlithium orvalproate therapy withinadequately controlled manic ormixed symptoms wererandomized to
receive risperidone, placebo, oranactive comparator, incombination withtheir original therapy.Risperidone, inadoserange of1to6mg/day, oncedaily, starting at2mg/day (mean modal doseof 3.8mg/day), combined withlithium orvalproate (inatherapeutic range of0.6mEq/L to1.4mEq/L or50mcg/mL to120mcg/mL, respectively) wassuperior tolithium orvalproate alone in
the reduction ofYMRStotal score.(2) Inasecond 3-week placebo-controlled combination trial, 142in-oroutpatients onlithium,valproate, orcarbamazepine therapy withinadequately controlled manic ormixed symptoms were
randomized toreceive risperidone orplacebo, incombination withtheir original therapy.Risperidone, inadoserange of1to6mg/day, oncedaily, starting at2mg/day (mean modal doseof 3.7mg/day), combined withlithium, valproate, orcarbamazepine (intherapeutic ranges of0.6mEq/L to1.4mEq/L forlithium, 50mcg/mL to125mcg/mL forvalproate, or4to12mcg/mL forcarbamazepine, respectively) wasnotsuperior tolithium, valproate, orcarbamazepine alone inthe
reduction ofYMRStotal score. Apossible explanation forthefailure ofthistrial wasinduction
of risperidone and9-hydroxyrisperidone clearance bycarbamazepine, leading tosubtherapeutic
levels ofrisperidone and9-hydroxyrisperidone.(1) Inoneofthe8-week, placebo-controlled trials, children andadolescents withautistic disorder
(n=101), aged5to16years, received twice daily doses ofplacebo orrisperidone 0.5to3.5mg/day onaweight-adjusted basis. Risperidone, starting at0.25mg/day or0.5mg/day depending
on baseline weight (<20kgand≥20kg,respectively) andtitrated toclinical response (meanmodal doseof1.9mg/day, equivalent to0.06mg/kg/day), significantly improved scores ontheABC-I subscale andontheCGI-C scale compared withplacebo.(2) Intheother 8-week, placebo-controlled trial inchildren withautistic disorder (n=55), aged5
to 12years, risperidone 0.02to0.06mg/kg/day given onceortwice daily, starting at0.01mg/kg/day andtitrated toclinical response (mean modal doseof0.05mg/kg/day, equivalent to1.4mg/day), significantly improved scores ontheABC-I subscale compared withplacebo.
Revised: 5/2011