WHO MODEL LIST OF ESSENTIAL MEDICINES APPLICATION

1. **Summary statement of the proposal for inclusion, change or deletion:**
   Inclusion of the tablet formulations of darunavir 75mg, 150mg, 300mg, and 600mg is proposed for treatment of multi-drug resistant HIV-1 among adults and children living with HIV/AIDS.

   The principal reasons for requesting this inclusion are as follows:

   1. Adults and children living with multi-drug resistant HIV-1 in resource-limited settings presently have limited options for their infection.

   2. WHO Guidelines recommend ritonavir-boosted darunavir (DRV/rtv) for third-line antiretroviral therapy (ART) in adults and in third/second-line ART in children.

   3. Treatment of HIV-1 will be improved with wider availability of these tablets.

2. **Name of the focal point in WHO submitting or supporting the application:**
   Marco Vitoria and Amitabh Suthar, WHO/HTM/HIV/ATC

3. **Name of the organization(s) consulted and/or supporting the application:**
   Tibotec BVBA
   Turnhoutseweg 30
   Beerse, 2340 Belgium
   Contact: Mercè Caturla, Global Regulatory Affairs

4. **International Nonproprietary Name (INN, generic name) of the medicine:**
   Darunavir

5. **Dosage form or strength proposed for inclusion:**
   In order to make HIV treatment regimens as patient and programme friendly as possible ATC proposes to manufacture scored tablets whenever possible

   - Darunavir 600 mg film-coated tablets (WHO and Tibotec supported)
   - Darunavir 300 mg film-coated tablets (WHO and Tibotec supported)
   - Darunavir 150 mg film-coated tablets (WHO supported)
   - Darunavir 75 mg film-coated tablets (WHO and Tibotec supported)

6. **International availability – sources, if possible manufacturers.**
   DRV 75mg, 150mg, 300mg, and 600 mg manufactured at:
   - Janssen Ortho, LLC
   - State Road 933
   - KM 0.1, Mamey Ward
   - Gurabo Puerto Rico 00778
   - Janssen-Cilag S.p.A
   - via C.Janssen
   - Borgo S Michele
   - 04010, Latina, Italy

   DRV 300mg and 600mg are also manufactured at:
   - Pharmacare Limited, trading as Aspen Pharmacare
7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group:**
   Since DRV is a protease inhibitor, inclusion within ‘Protease inhibitors’ (6.4.2.3) is requested.

8. **Information supporting the public health relevance**

   **8.1 Epidemiological information on disease burden**
   UNAIDS reported that as of December 2008, 95% of the world’s 33.4 million people living with HIV/AIDS (PLHIV) were in low and middle income countries. In 2008 there were 2.7 million new HIV-1 infections and two million AIDS-related deaths. The 2010 WHO Progress Report for HIV/AIDS indicated that at the end of 2009 there were approximately 5.25 million people in low and middle income countries on antiretroviral therapy (36% of those in need of therapy). Resistance to ART may emerge due to inappropriate prescribing of ART (monotherapy or dual therapy), treatment interruptions due to suboptimal patient adherence, poor patient retention on ART, or ART supply shortages or stock-outs at unacceptably high levels.

Darunavir, in combination with other antiretrovirals, is indicated for the treatment of HIV-1 in antiretroviral treatment-experienced adults and children 6 years of age and above. The target population is persons who are resistant to other antiretrovirals. These patients would usually be on the 3rd line therapy, but some children may be using it for second line therapy. Data to support the number of patients who require 3rd line treatment in resource limited settings is very limited due to poor monitoring of virological failures. Guidelines recommend clinical and/or immunological markers to detect ART failure but it is well documented that once this occurs, virological failure has been present for a prolonged period of time. Under such circumstances development of mutations to ARVs will be considerable, and will impact future treatment options.

If patients are allowed to fail ART, they will have detectable viral loads which harbour drug resistant virus, which can potentially be transmitted to other persons. Such new infections will require more 2nd or 3rd line ART for initial treatment. This will be more expensive than widely available 1st line regimens. Therefore, increasing access to third line regimens is critical to suppressing HIV-1 in persons with multi-drug resistant HIV-1.

Discussions on viral transmission and the role of ARVs have been very topical. The Swiss Federal Commission for HIV/AIDS has stated that if patients are on HAART then the likelihood of transmission is significantly reduced. There has also been mathematical modelling done to show if all HIV-1 patients are treated with ARVs then new infections are likely to fall to very low levels. Hence the need for continued treatment and virological suppression is paramount in controlling the epidemic. The need for ARVs like darunavir is important in managing treatment experienced patients.

**8.2 Assessment of current use**
Statistics on the number of persons on DRV are not collected, although cumulative exposure is estimated for pharmacovigilance (see Section 11).
8.3 Target population
HIV-1 infected adults who have failed WHO-recommended first and second line regimens.
HIV-1 infected children 6 years of age and above who have failed WHO-recommended first
line and/or second-line regimen.

9. Treatment details:

9.1 Reference to existing WHO and other clinical guidelines

The 2010 WHO adult antiretroviral therapy guidelines make the following recommendations
for third-line regimens:

1. National programmes should develop policies for third-line therapy that consider funding,
sustainability, and the provision of equitable access to ART.
   (Conditional recommendation, low quality of evidence)
2. Third-line regimens should include new drugs likely to have anti-HIV-1 activity, such as
   integrase inhibitors and second-generation NNRTIs and PIs.
   (Conditional recommendation, low quality of evidence)
3. Patients on a failing second-line regimen with no new ARV options should continue with
   a tolerated regimen.
   (Conditional recommendation, very low quality of evidence)

The 2010 WHO infant and children antiretroviral therapy guidelines make the following
recommendations for third-line regimens:

1. Strategies that balance benefits and risks for children need to be explored in the event of
   second line treatment failure.
2. For older children who have more therapeutic options available to them, it may be
   possible to construct third-line ARV regimens using novel drugs used in the treatment of
   adults such as darunavir and raltegravir.
3. Children on a failing second-line regimen with no new ARV options should continue with
   a tolerated regimen.
4. When stopping ART may have to be considered, the prevention of OIs, relief of
   symptoms and management of pain needs to continue.

9.2 Dosage regimen
Darunavir must always be given with low dose ritonavir as a pharmacokinetic enhancer and
in combination with other antiretroviral medicinal products.

Antiretroviral treatment experienced adults:
DRV 600mg twice daily and ritonavir (rtv) 100mg twice daily with food.

Hepatic impairment: No dose adjustment is required in patients with mild or moderate
hepatic impairment. There are no data regarding the use of darunavir/rtv when
co-administered to patients with severe hepatic impairment; therefore, specific dosage
recommendations cannot be made. Darunavir/rtv should be used with caution in patients
with severe hepatic impairment.

Renal impairment: No dose adjustment is required in patients with renal impairment.
Antiretroviral treatment-experienced paediatric patients (6 to < 18 years of age):
The recommended dose of darunavir/rtv for paediatric patients (6 to < 18 years of age and
weighing at least 20 kg) is based on body weight and should not exceed the recommended
adult dose (600/100 mg b.i.d.). Darunavir/rtv should be taken with food.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20 kg–&lt; 30 kg</td>
<td>375 mg darunavir/50 mg ritonavir b.i.d.</td>
</tr>
<tr>
<td>≥ 30 kg–&lt; 40 kg</td>
<td>450 mg darunavir/60 mg ritonavir b.i.d.</td>
</tr>
<tr>
<td>≥ 40 kg</td>
<td>600 mg darunavir/100 mg ritonavir b.i.d.</td>
</tr>
</tbody>
</table>

9.3 Need for special diagnostic or treatment facilities and skills
Not needed

10. Summary of comparative effectiveness in a variety of clinical settings:

Studies assessing effect of DRV/rtv in treatment-experienced adults:

**TITAN** is a randomised, controlled, open-label Phase III trial comparing darunavir/rtv
600/100 mg b.i.d. versus lopinavir/rtv 400/100 mg b.i.d. in antiretroviral - experienced,
lopinavir/rtv naïve HIV-1 infected adult patients. Both arms used an optimised background
regimen (OBR) consisting of ≥ 2 antiretrovirals (NRTIs with or without NNRTIs). HIV-1
infected patients who were eligible for this trial had plasma HIV-1 RNA > 1,000 copies/mL
and were on a highly active antiretroviral therapy regimen (HAART) for ≥ 12 weeks.

Virologic response was defined as a confirmed plasma HIV-1 RNA viral load < 400 copies/ml.
Analyses included 595 patients in the TITAN trial who had completed 96 weeks of treatment
or discontinued earlier. Demographics and baseline characteristics were balanced between the
darunavir/rtv arm and the lopinavir/ritonavir arm. The 298 patients on darunavir/rtv
600/100 mg b.i.d. had a median age of 40 years (range 18-68), 77% were male, 54% white, 18%
black, 15% hispanic, and 9% asian. The mean baseline plasma HIV-1 RNA was
4.33 log_{10} copies/ml and the median baseline CD4+ cell count was 235 x 10^6 cells/l
(range 3-831 x 10^6 cells/l).

In the 48-week analysis, virologic response, defined as the percentage of subjects with plasma
HIV-1 RNA level < 400 copies/ml, was 76.5% and 67.0% for the darunavir/rtv arm and
lopinavir/rtv arm, respectively. Non-inferiority in virologic response was demonstrated
(p < 0.001) for both ITT and OP population, furthermore superiority of darunavir/rtv over
the lopinavir/rtv arm was demonstrated (p = 0.008). 70.8% of patients on darunavir/rtv
reached less than 50 HIV-1 RNA copies/ml versus 60.3% in the lopinavir/rtv arm.

Analyses of data at 96 weeks of treatment in the TITAN trial demonstrated sustained
antiretroviral efficacy and immunological benefit. In the 96-week analysis, virologic response,
defined as the percentage of subjects with plasma HIV-1 RNA level < 400 copies/ml, was
66.8% and 58.9% for the darunavir/rtv arm and lopinavir/rtv arm, respectively.
Non-inferiority in virologic response was demonstrated (p < 0.001) for both ITT and OP
population, furthermore superiority of darunavir/rtv over the lopinavir/rtv arm was
demonstrated (p = 0.034 for the ITT population and p = 0.033 for the OP population). 60.4%
of patients on darunavir/rtv reached HIV-1 RNA less than 50 copies/ml versus 55.2% in the lopinavir/rtv arm. The table below shows the efficacy data of the 48-week and 96-week analyses from the TITAN trial:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>At week 48a</th>
<th>At week 96b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRV/rtv + OBR, N=298</td>
<td>LPV/rtv + OBR, N=297</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 400 copies/mlc</td>
<td>228 (76.5%)</td>
<td>199 (67.0%)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mlc</td>
<td>211 (70.8%)</td>
<td>179 (60.3%)</td>
</tr>
<tr>
<td>mean HIV-1 RNA log change from baselinec</td>
<td>-1.95</td>
<td>-1.72</td>
</tr>
<tr>
<td>median CD4+ cell count change from baseline (x 10^6/l)e</td>
<td>88</td>
<td>81</td>
</tr>
</tbody>
</table>

a Data based on analyses at week 48  
b Data based on analyses at week 96  
c Imputations according to the TLOVR algorithm  
d Based on a normal approximation of the difference in % response  
e NC=F  
f Difference in means

**POWER 1 and POWER 2** are randomised, controlled Phase IIb trials in adult patients with a high level of PI resistance, consisting of 2 parts: an initial partially blinded, dose-finding part and a second long term part in which all patients randomised to darunavir/rtv received the recommended dose of 600/100 mg b.i.d. HIV-1 infected patients who were eligible for these trials had plasma HIV-1 RNA > 1,000 copies/ml, had prior treatment with PI(s), NNRTI(s) and NRTI(s), had at least 1 primary (i.e. major) PI mutation at screening and were on a stable PI-containing regimen at screening for at least 8 weeks. Randomisation was stratified by the number of PI mutations, screening viral load and the use of enfuvirtide.

Demographics and baseline characteristics were balanced between the darunavir/rtv arm and the comparator arm. In both trials combined, the 131 patients on darunavir/rtv 600/100 mg b.i.d. had a median age of 43 years (range 27-73), 89% were male, 81% white, 10% black and 7% hispanic. The mean baseline plasma HIV-1 RNA was 4.61 log_{10} copies/ml and the median baseline CD4+ cell count was 153 x 10^6 cells/l (range 3 – 776 x 10^6 cells/l). The median darunavir FC was 4.3. In the darunavir/rtv 600/100 mg b.i.d. arm patients had prior exposure to a mean of 4 PIs, 5 NRTIs and 1 NNRTI versus 4 PIs, 6 NRTIs and 1 NNRTI in the comparator arm. Twenty percent of the patients in the darunavir/rtv arm had prior use of enfuvirtide versus 17% in the comparator arm.

The virologic response, defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log_{10} versus baseline, was evaluated in patients receiving darunavir/rtv plus an optimised background regimen (OBR) versus a control arm receiving an investigator-selected PI(s) regimen plus an OBR. The OBR consisted of at least 2 NRTIs with or without enfuvirtide (ENF). Based on resistance
testing and prior medical history, selected PIs in the control arm included: lopinavir/ritonavir in 36%, (fos)amprenavir in 34%, saquinavir in 35% and atazanavir in 17%. Twenty-three percent of the control patients used dual-boosted PIs. Approximately 47% of all patients used enfuvirtide and 35% of the use was in patients who were ENF-naïve.

**POWER 3**

additional data on the efficacy of darunavir/rtv 600/100 mg b.i.d. have been obtained in treatment-experienced adult patients participating in the non-randomised trial TMC114-C215. At week 48, 334 patients were included in the POWER 3 efficacy analysis who had initiated therapy with darunavir/rtv with the recommended dose of 600/100 mg b.i.d. The OBR consisted of at least two NRTIs with or without enfuvirtide. Entry criteria were the same as and baseline characteristics were comparable to those of POWER 1 and POWER 2. The mean baseline plasma HIV-1 RNA was 4.58 log₁₀ copies/ml and the median CD4+ cell count was 120 x 10⁶ cells/l (range 0 – 831 x 10⁶ cells/l). The median darunavir FC was 3.2. Patients had a prior exposure to a mean of 5 PIs, 6 NRTIs and 2 NNRTIs, 32% had prior use of enfuvirtide.

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>POWER 1 and POWER 2 pooled data</th>
<th>POWER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>DRV/rtv, N=131</strong></td>
<td><strong>Control, N=124</strong></td>
</tr>
<tr>
<td>HIV-1 RNA log₁₀ mean change from baseline (log₁₀ copies/ml)</td>
<td>-1.69</td>
<td>-0.37</td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 1 log₁₀ below baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 400 copies/ml</td>
<td>81 (61.8%)</td>
<td>20 (16.1%)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/ml</td>
<td>72 (55.0%)</td>
<td>18 (14.5%)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/ml</td>
<td>59 (45.0%)</td>
<td>14 (11.3%)</td>
</tr>
<tr>
<td>CD4+ cell count mean change from baseline (x 10⁶/l)</td>
<td>103</td>
<td>17</td>
</tr>
</tbody>
</table>

- Non-completer is failure imputation: patients who discontinued prematurely are imputed with a change equal to 0
- P-values < 0.001, based on the ANOVA model
- Last Observation Carried Forward imputation
- Imputations according to the TLOVR algorithm
- Confidence interval around observed differences of response rates; P-values < 0.001, based on the logistic regression model.

In the pooled POWER 1 and POWER 2 analysis, the proportion of patients in the darunavir/rtv (600/100 mg b.i.d.) arm provided superior decreases in log₁₀ viral load from baseline compared to the comparator arm. At week 48, the proportion of patients in the darunavir/rtv arm resulted in 62% of patients with a decrease of at least 1.0 log₁₀ in viral load, compared to 16% in the comparator arm. The proportion of patients with HIV-1 RNA < 50 copies/ml was 45% in the darunavir/rtv arm compared to 11% for the comparator arm.
The 48-week efficacy POWER 3 analysis confirmed the viral load reduction and CD4+ increase observed in the POWER 1 and POWER 2 trials. Of the 334 patients included in the 48-week analysis, 59% had a virologic response defined as a decrease of at least 1.0 log₁₀ in plasma viral load versus baseline and 46% of the patients reached less than 50 HIV-1 RNA copies/ml.

Analyses of data through 96 weeks of treatment in the POWER trials demonstrated sustained antiretroviral efficacy and immunological benefit. Treatment with darunavir/rtv (600/100 mg b.i.d.) resulted in 56.5% (POWER 1 and 2) and 52.2% (POWER 3) of patients with a decrease of at least 1 log₁₀ in HIV-1 RNA from baseline. 38.9% (POWER 1 and 2) and 42.1% (POWER 3) of patients reached an HIV-1 RNA level < 50 copies/ml. At 96 weeks, 49.6% (POWER 1 and 2) and 50.0% (POWER 3) of patients reached less than 400 HIV-1 RNA copies/ml. The mean decrease in HIV-1 RNA level compared to baseline was 1.58 (POWER 1 and 2) and 1.43 (POWER 3) log₁₀ copies/ml and a mean increase in CD4+ cell count of 133 x 10⁶ cells/l (POWER 1 and 2) and 103 x 10⁶ cells/l (POWER 3) was observed. Out of the 206 patients who responded with complete viral suppression (< 50 copies/ml) at week 48, 177 patients (86% of the responders at week 48) remained responders at week 96.

Studies assessing effect of DRV/rtv in treatment-experienced children:
DELPHI² is an open-label, Phase II trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of darunavir/rtv in 80 antiretroviral treatment-experienced HIV-1 infected paediatric patients aged 6 to 17 years and weighing at least 20 kg. At week 24, the virologic response rate was evaluated in paediatric patients receiving darunavir/rtv in combination with other antiretroviral agents. Virologic response was defined as a decrease in plasma HIV-1 RNA viral load of at least 1.0 log₁₀ versus baseline. The mean baseline plasma HIV-1 RNA was 4.64 log₁₀ copies/ml, and the median baseline CD4+ cell count was 330 x 10⁶ cells/l (range: 6 to 1,505 x 10⁶ cells/l).

At week 24, 73.8% of the paediatric patients had at least 1.0 log₁₀ HIV-1 RNA decrease from baseline. The proportion of paediatric patients reaching undetectable viral load (< 50 HIV-1 RNA copies/ml) was 50.0%, and the proportion of paediatric patients with < 400 HIV-1 RNA copies/ml was 63.8%. The mean change in plasma HIV-1 RNA from baseline was -1.98 log₁₀ copies/ml. The mean CD4+ cell count increase from baseline was 117 x 10⁶ cells/l.

11. Summary of comparative evidence on safety:

11.1 Estimate of total patient exposure to date
In the clinical trials, cumulatively, up to the data-lock date of 23 December 2009, a total number of 18,413 adult and 241 subjects less than 18 years of age were exposed to darunavir (clinical supply) in the context of Company-sponsored trials, Early Access programs or known Cross-Company sponsored trials. Post-marketing cumulative estimated exposure is 1,358,284 person-months.

11.2 Description of adverse effects/reactions
Adverse reactions reported in 2% or more of patients receiving darunavir/rtv include: headache, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, rash, lipodystrophy (lipo hypertrophy, lipodystrophy and lipoatrophy), asthenia, fatigue and increased lipids.

Adverse reactions reported in less than 2% of patients receiving darunavir/rtv include: acute pancreatitis, flatulence, angioedema, pruritus, Stevens-Johnson Syndrome, urticaria, myalgia,
11.3 Identification of variation in safety due to health systems and patient factors
No clinically significant differences in safety have been identified due to differences in health systems and patient factors.

11.4 Summary of comparative safety against comparators
Please see appendix two for a table describing the adverse reactions seen in treatment-experienced patients on LPV/rtv 400/100 mg b.i.d. and DRV/rtv 600/100 mg b.i.d.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

12.1 Range of costs of the proposed medicine
The company has signed a royalty-free voluntary license and partnership agreement with the generic manufacturer Aspen Pharmacare to provide access to DRV in sub-Saharan Africa. As a result of the agreement there will be a single co-branded product in sub-Saharan Africa, distributed by Aspen Pharmacare and sold at an ex-factory price that should not exceed US$2.5 a day. The product is offered on an FOB basis – incoterm 2000. Additional costs may include the logistics fee in South Africa, or the freight, insurance, customs handling, taxes and duties, and other costs levied at the discretion of national authorities and other respective entities in the other sub Saharan countries and least developed countries, which are beyond the control of Aspen Pharmacare and Tibotec Pharmaceuticals. Local retail prices may therefore be higher.

In middle income countries, the company works with local health authorities to enable prompt regulatory approval and inclusion in the National AIDS program and/or HIV/AIDS treatment guidelines. Middle-income country prices for DRV reflect a substantial reduction from those in the U.S.A. and Western Europe and reflect health authorities’ assessments of patient need for DRV in these countries based on the local label indication. In view of the initial indication for treatment of highly treatment experienced patients, demand in developing countries as well as funding by Global Fund and /or PEPFAR has been low. The information in the International Drug Price Indicator Guide as well as the Global Price Reporting Mechanism is thus based and a limited number of transactions, and does not provide an appropriate average price in Middle Income Countries.

MSF lists the yearly price of DRV as USD 1095. The international drug price indicator guide lists the yearly price of DRV as USD 1150. The WHO Global Price Reporting Mechanism reports the lowest yearly price of DRV to be USD 1095.

12.2 Comparative cost-effectiveness (presented as range of cost per routine outcome)
The cost-effectiveness studies in this section focus on evidence from the developed world, and are available from multiple countries perspectives, including U.S.A., Canada and several European countries, and are based on the clinical efficacy data gathered in the POWER and TITAN adult trials. The results may not necessarily be applicable to resource-poor countries, due to different health care settings and unit costs for anti-retroviral drugs and other health care
resources. There are no analyses that specifically assess the cost-effectiveness of darunavir for the treatment of experienced patients in resource-poor settings. In addition, currently no economic evaluations have been carried out in a paediatric population.

Mauskopf et al (2010) provides an overview of several different economic analyses that investigate the cost-effectiveness of DRV/rtv 600/100 mg b.i.d. for treatment-experienced adults. These analyses include incremental cost-utility analyses (incremental cost/QALY), analyses of cost-effectiveness using HIV-1-specific efficacy endpoints (mean and incremental annual ARV drug cost per patient with an undetectable plasma HIV-1 RNA), and calculation of direct costs of care (including drug costs plus other health care costs) per patient for the first year after starting treatment with DRV/rtv-based treatment. In summary, the economic evaluations confirm that DRV/rtv 600/100 mg b.i.d. not only has major clinical benefits, but also has been shown to have a favourable economic profile for the management of HIV-1-infected, treatment-experienced adults.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well).

Darunavir 300 mg tablet Marketing Authorization was first granted by the Food and Drug Administration (FDA) on 23 June 2006. The European Medicines Agency (EMA) granted Marketing Authorization to darunavir 300 mg tablets on 12 February 2007. Besides these registrations, more than 60 countries in other regions have granted local Marketing Authorisation.

Darunavir 600 mg tablet Marketing Authorization was first granted by the Food and Drug Administration (FDA) on 25 February 2008. The European Medicines Agency (EMA) granted Marketing Authorization to darunavir 600 mg tablets on 29 January 2009. Besides these registrations, more than 20 countries in other regions have granted local Marketing Authorisation.

Darunavir 75 mg and 150 mg tablet Marketing Authorization was first granted by the Food and Drug Administration (FDA) on 18 December 2008. The European Medicines Agency (EMA) granted Marketing Authorization to darunavir 75 mg and 150 mg tablets on 23 June 2009. Besides these registrations, more than 7 countries in other regions have granted local Marketing Authorisation.


International Pharmacopoeia

15. Proposed (new/adapted) text for the WHO Model Formulary

*Note the AHFS Drug Information book was used as a reference for this section.

**Dosage forms:** 75mg, 150mg, 300mg, and 600mg film-coated tablets

**Description:** Darunavir is a second-generation protease inhibitor
**Uses:** Treatment of HIV-1 in combination with other antiretrovirals in third-line therapy for adults. Treatment of HIV-1 in combination with at least two other antiretrovirals in second or third line therapy for children 6 years of age and above.

**Contraindications:** Hypersensitivity to darunavir or to any of the excipients.

Darunavir/rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events. These medicinal products include astemizole, alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), terfenadine, midazolam, triazolam, cisapride, pimozide and the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine).

**Precautions:** Darunavir/rtv should not be used in children below 3 years of age given toxicity was observed in juvenile rats aged 23 to 26 days dosed with darunavir (from 20 mg/kg to 1,000 mg/kg).

**Severe skin reactions**
During the clinical development program (N=3,063), severe skin reactions, which may be accompanied with fever and/or elevations of transaminases, have been reported in 0.4% of patients. Stevens-Johnson Syndrome has been rarely (<0.1%) reported; and during post-marketing experience toxic epidermal necrolysis has been reported very rarely (<0.01%). Discontinue darunavir immediately if signs or symptoms of severe skin reactions develop. These can include but are not limited to severe rash or rash accompanied with fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, hepatitis and/or eosinophilia.

Rash (all grades, regardless of causality) occurred in 10.3% of patients treated with darunavir. Rash was mostly mild-to-moderate, often occurring within the first four weeks of treatment and resolving with continued dosing. The discontinuation rate due to rash in patients using darunavir/rtv was 0.5%.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing darunavir/rtv + raltegravir compared to subjects receiving darunavir/rtv without raltegravir. However, rash that was considered drug related occurred at similar rates for all three groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

Darunavir contains a sulfonamide moiety. Darunavir should be used with caution in patients with a known sulfonamide allergy. In clinical studies with darunavir/rtv, the incidence and severity of rash was similar in patients with or without a history of sulfonamide allergy.

**Hepatotoxicity**
Drug-induced hepatitis (e.g. acute hepatitis, cytolytic hepatitis) has been reported with darunavir/rtv. During the clinical development program (N=3,063), hepatitis was reported in 0.5% of patients receiving combination therapy with darunavir/rtv. Patients with pre-existing liver dysfunction, including chronic active hepatitis B or C, have an increased risk for liver function abnormalities including severe hepatic adverse events.
Appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/rtv and patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pre-treatment elevations of transaminases, especially during the first several months of darunavir/rtv treatment.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of liver enzymes and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on darunavir/rtv should prompt consideration of interruption or discontinuation of treatment.

**Interactions with medicinal products**
Rifampicin may decrease darunavir plasma concentrations to subtherapeutic levels, therefore this combination of medications should not be used concomitantly.

St John’s wort (hypericum perforatum) may decrease darunavir plasma concentrations to subtherapeutic levels, therefore this combination of medications should not be used concomitantly.

**Doses:**
Antiretroviral treatment-experienced adults: darunavir 600 mg twice daily and ritonavir 100 mg twice daily with food and other antiretrovirals.

Antiretroviral treatment-experienced paediatric patients (6 to 17 years of age): The recommended paediatric (6 to 17 years of age and weighing at least 20 kg) doses are weight-based and should be taken with food. Doses should not exceed the recommended adult dose and must be in combination with other antiretrovirals.

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 20 kg–&lt; 30 kg</td>
<td>375 mg darunavir/50 mg ritonavir</td>
</tr>
<tr>
<td></td>
<td>b.i.d.</td>
</tr>
<tr>
<td>≥ 30 kg–&lt; 40 kg</td>
<td>450 mg darunavir/60 mg ritonavir</td>
</tr>
<tr>
<td></td>
<td>b.i.d.</td>
</tr>
<tr>
<td>≥ 40 kg</td>
<td>600 mg darunavir/100 mg ritonavir</td>
</tr>
<tr>
<td></td>
<td>b.i.d.</td>
</tr>
</tbody>
</table>

The safety and efficacy of darunavir/rtv in antiretroviral treatment-experienced children aged 3 to less than 6 years and in antiretroviral treatment naïve paediatric patients have not been established.

**Adverse effects:** Adverse events reported in 2% or more of patients receiving darunavir/rtv include: headache, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, rash, lipodystrophy (lipohypertrophy, lipodystrophy and lipoatrophy), asthenia, fatigue and increased lipids.
Adverse events reported in less than 2% of patients receiving darunavir/rtv include: acute pancreatitis, flatulence, angioedema, pruritus, Stevens-Johnson Syndrome, urticaria, myalgia, osteonecrosis, anorexia, diabetes mellitus, (drug) hypersensitivity, immune reconstitution syndrome, acute hepatitis, gynaecomastia, abnormal dreams.

**Pregnancy:** The United States Food and Drug Administration categorized DRV as class C. There are no adequate and well-controlled studies with darunavir in pregnant women. Studies in animals have not shown evidence of developmental toxicity or effect on reproductive function and fertility. Darunavir/rtv should be used during pregnancy only if the potential benefit justifies the potential risk.

**Breastfeeding:** It is not known whether darunavir is excreted in human milk. Studies in rats have demonstrated that darunavir is excreted in milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse events in nursing infants, mothers should be instructed not to breastfeed if they are receiving darunavir.

**Hepatic impairment:** There are no data regarding the use of darunavir/rtv when co-administered to patients with severe hepatic impairment; therefore, specific dosage recommendations cannot be made. Darunavir/rtv should be used with caution in patients with severe hepatic impairment. Based on data that demonstrated that the steady-state pharmacokinetic parameters of darunavir in subjects with mild and moderate hepatic impairment were comparable with those in healthy subjects, no dose adjustment is required in patients with mild or moderate hepatic impairment.

**Renal impairment:** Since the renal clearance of darunavir is limited, a decrease in total body clearance is not expected in patients with renal impairment. As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.

**Drug interactions:** Darunavir and ritonavir are both inhibitors of the CYP3A isoform. Co-administration of darunavir and ritonavir and medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events. Detailed information in appendix 3.
### Appendix 1. List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine transaminase</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate transaminase</td>
</tr>
<tr>
<td>ATC</td>
<td>Antiretroviral Treatment and Care</td>
</tr>
<tr>
<td>b.i.d.</td>
<td>bis in die ; twice daily</td>
</tr>
<tr>
<td>CD4+</td>
<td>cluster of differentiation 4 positive</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450</td>
</tr>
<tr>
<td>DRV</td>
<td>darunavir</td>
</tr>
<tr>
<td>DRV/rtv</td>
<td>darunavir boosted with ritonavir</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>ENF</td>
<td>enfuvirtide</td>
</tr>
<tr>
<td>FC</td>
<td>fold change</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FOB</td>
<td>free on board</td>
</tr>
<tr>
<td>HAART</td>
<td>highly active antiretroviral therapy</td>
</tr>
<tr>
<td>HIV-1</td>
<td>human immunodeficiency virus type 1</td>
</tr>
<tr>
<td>HTM</td>
<td>HIV/AIDS, Tuberculosis, and Malaria</td>
</tr>
<tr>
<td>INN</td>
<td>international nonproprietary name</td>
</tr>
<tr>
<td>ITT</td>
<td>intent-to-treat</td>
</tr>
<tr>
<td>LPV/rtv</td>
<td>lopinavir boosted with ritonavir</td>
</tr>
<tr>
<td>MSF</td>
<td>Médecins Sans Frontières</td>
</tr>
<tr>
<td>NC=F</td>
<td>non-completer equals failure</td>
</tr>
<tr>
<td>NNRTI</td>
<td>non-nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NRTI</td>
<td>nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>OBR</td>
<td>optimised background regimen</td>
</tr>
<tr>
<td>OI</td>
<td>opportunistic infections</td>
</tr>
<tr>
<td>OP</td>
<td>on-protocol</td>
</tr>
<tr>
<td>PEPFAR</td>
<td>President’s Emergency Plan for AIDS Relief</td>
</tr>
<tr>
<td>PI</td>
<td>protease inhibitor</td>
</tr>
<tr>
<td>PLHIV</td>
<td>people living with hiv</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-years</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>rtv</td>
<td>ritonavir</td>
</tr>
<tr>
<td>TLOVR</td>
<td>time to loss of virologic response</td>
</tr>
<tr>
<td>TMC</td>
<td>Tibotec Medicinal Compound</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
### Appendix 2. Adverse drug reactions reported in TITAN at 96 weeks

<table>
<thead>
<tr>
<th>Adverse drug reactions*</th>
<th>DRV/rtv + OBR#, N=298</th>
<th>LPV/rtv + OBR#, N=297</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.7%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14.4%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.0%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipodystrophy (lipohypertrophy, lipodystrophy, and lipoatrophy)</td>
<td>5.4%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rash</td>
<td>5.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0.3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.7%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>3.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune reconstitution syndrome</td>
<td>0.3%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Reproductive system and breast disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>0.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Excluding laboratory abnormalities reported as ADRs. #OBR, Optimised Background Regimen.
Appendix 3. Drug interactions

*alfuzosin       Increased risk of serious and/or life-threatening events
*amiodarone     Plasma concentration of amiodarone increased
*astemizole     Increased risk of serious and/or life-threatening events
atorvastatin    Plasma concentration of atorvastatin increased
*bepridil       Plasma concentration of bepridil increased
bosentan        Plasma concentration of bosentan increased
buprenorphine   Plasma concentration of the metabolite norbuprenorphine increased
carbamazepine   Plasma concentration of carbamazepine increased
*cisapride      Plasma concentration of cisapride increased
clarithromycin  Plasma concentration of clarithromycin increased
colicinicine    Plasma concentration of colcicinie increased
cyclosporine    Plasma concentration of cyclosporine increased
*dexamethasone (systemic) Plasma concentration of dexamethasone decreased
digoxin         Plasma concentration of digoxin increased
*dihydroergotamine Increased risk of serious and/or life-threatening events
efavirenz       Plasma concentration of efavirenz increased; plasma concentration of darunavir decreased
*ergonovine     Increased risk of serious and/or life-threatening events
*ergotamine     Increased risk of serious and/or life-threatening events
ethinylestradiol Plasma concentration of ethinylestradiol decreased
etravirine      Plasma concentration of etravirine decreased
*felodipine     Plasma concentration of felodipine increased
*fluticasone    Plasma concentration of fluticasone increased
indinavir       Plasma concentration of indinavir increased; plasma concentration of darunavir increased
itraconazole    Plasma concentration of darunavir increased; plasma concentration of itraconazole increased
ketoconazole    Plasma concentration of darunavir increased; plasma concentration of ketoconazole increased
*lidocaine (systemic) Plasma concentration of lidocaine increased
*lomipinavir/ritonavir Plasma concentration of darunavir decreased
*lovastatin     Increased risk of myopathy, including rhabdomyolysis
maraviroc       Plasma concentration of maraviroc increased
methadone       Plasma concentration of methadone increased
*methylergonovine Increased risk of serious and/or life-threatening events
*midazolam      Increased risk of serious and/or life-threatening events
nevirapine      Plasma concentration of nevirapine increased
*nicardipine    Plasma concentration of nicardipine increased
*nifedipine     Plasma concentration of nifedipine increased
norethindrone   Plasma concentration of norethindrone decreased
paroxetine      Plasma concentration of paroxetine decreased
*phenobarbital  Plasma concentration of darunavir decreased
*phenytoin      Plasma concentration of darunavir decreased
*pimozide       Increased risk of serious and/or life-threatening events
pravastatin     Plasma concentration of pravastatin increased
*quinidine      Plasma concentration of quinidine increased
rifabutin: Plasma concentration of darunavir increased; plasma concentration of rifabutin increased

*rifampin: Plasma concentration of darunavir decreased

rosvastatin: Plasma concentration of rosuvastatin increased

*salmeterol: Increased risk of QT prolongation, palpitations and sinus tachycardia

*saquinavir: Plasma concentration of darunavir decreased

sertraline: Plasma concentration of sertraline decreased

*sildenafil (when used for pulmonary arterial hypertension): Increased risk of serious and/or life-threatening events

sildenafil (when used for erectile dysfunction): Plasma concentration of sildenafil increased

*simvastatin: Increased risk of myopathy, including rhabdomyolysis

sirolimus: Plasma concentration of sirolimus increased

*St John’s wort: Plasma concentration of darunavir decreased

tacrolimus: Plasma concentration of tacrolimus increased

tadalafil: Plasma concentration of tadalafil increased

tenofovir disoproxil fumarate: Plasma concentration of tenofovir increased

*terfenadine: Increased risk of serious and/or life-threatening events

*triazolam: Increased risk of serious and/or life-threatening events

vardenafil: Plasma concentration of vardenafil increased

*voriconazole: Plasma concentration of darunavir increased; plasma concentration of voriconazole decreased

warfarin: Plasma concentration of warfarin affected

* indicates a potentially hazardous interaction and the combined administration of the drugs involved should be avoided, or only be taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences but dose adjustments may be needed. In case of no interaction, drugs are not listed.

Darunavir and ritonavir are both inhibitors of the CYP3A isoform. Co-administration of darunavir and ritonavir and medicinal products primarily metabolized by CYP3A may result in increased plasma concentrations of such medicinal products, which could increase or prolong their therapeutic effect and adverse events.

Darunavir /rtv should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which increased plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These medicinal products include astemizole, alfuzosin, sildenafil (when used for treatment of pulmonary arterial hypertension), terfenadine, midazolam, triazolam, cisapride, pimozide and the ergot alkaloids (e.g., ergotamine, dihydroergotamine, ergonovine and methylergonovine).

Rifampicin is a potent inducer of CYP450 metabolism. Darunavir/rtv should not be used in combination with rifampicin, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir.

Darunavir /rtv should not be used concomitantly with products containing St John’s wort (Hypericum perforatum) because co-administration may cause significant decreases in darunavir plasma concentrations.
concentrations. This may result in loss of therapeutic effect to darunavir.

**Antiretroviral medicinal products**

**Nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs)**

**Didanosine**
Darunavir / rtv (600/100 mg b.i.d.) did not significantly affect didanosine exposure. The combination of darunavir co-administered with low dose ritonavir and didanosine can be used without dose adjustments.

As it is recommended that didanosine be administered on an empty stomach, didanosine should be administered 1 hour before or 2 hours after darunavir/rtv (which are administered with food).

**Tenofovir**
The results of an interaction trial with tenofovir (tenofovir disoproxil fumarate 300 mg once daily [q.d.]) demonstrated that the systemic exposure of tenofovir was increased by 22% when co-administered with darunavir/rtv (300/100 mg b.i.d.). This finding is not considered to be clinically relevant. There was no change in the urinary excretion of tenofovir or darunavir during co-administration. Tenofovir did not have a significant influence on darunavir exposure. No dose adjustments of darunavir, ritonavir, or tenofovir disoproxil fumarate are required when these drugs are co-administered.

**Other NRTIs**
Based on the different elimination pathways of the other NRTIs (zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir) that are primarily renally excreted, no drug interactions are expected for these medicinal compounds and darunavir/rtv.

**Non-nucleoside reverse transcriptase inhibitors (NNRTIs)**

**Etravirine**
In an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and etravirine, there was a 37% decrease in etravirine exposure in the presence of darunavir/rtv and no relevant change in exposure to darunavir. Therefore, darunavir/rtv can be co-administered with etravirine 200 mg b.i.d. without dose adjustments.

**Efavirenz**
An interaction trial between darunavir/rtv (300/100 mg b.i.d.) and efavirenz (600 mg q.d.) has been performed. In the presence of efavirenz, a decrease of 13% for darunavir exposure was observed. Exposure to efavirenz was increased by 21% when administered in combination with darunavir/rtv. Since this difference is considered not to be clinically relevant, the combination of darunavir/rtv and efavirenz can be used without dose adjustments.

**Nevirapine**
The results of an interaction trial with darunavir/rtv (400/100 mg b.i.d.) and nevirapine (200 mg b.i.d.) demonstrated that darunavir exposure was not affected when administered concomitantly with nevirapine. Exposure to nevirapine increased by 27% (compared to historical controls) when administered in combination with darunavir/rtv. Since this difference is not considered to be clinically relevant, the combination of darunavir/rtv and nevirapine can be used without dose adjustments.
Protease inhibitors (PIs)

Ritonavir
The overall pharmacokinetic enhancement effect by ritonavir was an approximate 14-fold increase in the systemic exposure of darunavir when a single dose of 600 mg darunavir was given orally in combination with ritonavir at 100 mg b.i.d. Therefore, darunavir should only be used in combination with low dose ritonavir as a pharmacokinetic enhancer.

Lopinavir/ritonavir
Results of interaction trials with darunavir with or without ritonavir and lopinavir/ritonavir (1,200 mg darunavir b.i.d. with or without 100 mg ritonavir b.i.d. and lopinavir/ritonavir 400/100 mg b.i.d. or 533/133.3 mg b.i.d.) demonstrated a decrease in the exposure (AUC) of darunavir by 40%. The appropriate doses of the combination have not been established. Hence, it is not recommended to co-administer darunavir/rtv with lopinavir/ritonavir.

Saquinavir
In an interaction trial between darunavir (400 mg b.i.d.), saquinavir (1,000 mg b.i.d.) and ritonavir (100 mg b.i.d.), darunavir exposure was decreased by 26% in the presence of saquinavir/rtv; saquinavir exposure was not affected by the presence of darunavir/rtv. It is not recommended to combine saquinavir and darunavir, with or without low dose ritonavir.

Atazanavir
An interaction trial between darunavir/rtv (400/100 mg b.i.d.) and atazanavir (300 mg q.d.) demonstrated that systemic exposure to darunavir and atazanavir was not significantly affected when co-administered. Atazanavir can be co-administered with darunavir/rtv.

Indinavir
In an interaction trial between darunavir/rtv (400/100 mg b.i.d.) and indinavir (800 mg b.i.d.), darunavir exposure was increased by 24% in the presence of indinavir/rtv; indinavir exposure was increased by 23% in the presence of darunavir/rtv. When used in combination with darunavir/rtv, dose adjustment of indinavir from 800 mg b.i.d. to 600 mg b.i.d. may be warranted in case of intolerance.

Other protease inhibitors
The co-administration of darunavir/rtv and PIs other than lopinavir/ritonavir, saquinavir, atazanavir and indinavir have not been studied. Therefore, such co-administration is not recommended.

CCR5 antagonist
When used in combination with darunavir/rtv, the dose of maraviroc should be 150 mg twice daily. An interaction trial between darunavir/rtv (600/100 mg b.i.d.) and maraviroc (150 mg b.i.d.) demonstrated that in the presence of darunavir/rtv the exposure of maraviroc was increased by 305%. There was no apparent effect of maraviroc on darunavir/ritonavir exposure.

Other medicinal products

Antiarrhythmics (bepridil, systemic lidocaine, quinidine and amiodarone)
Exposure to bepridil, lidocaine, quinidine and amiodarone may be increased when co-administered with darunavir/rtv. Caution is warranted and therapeutic drug monitoring of antiarrhythmics is
recommended when available.

**Digoxin**
An interaction trial with darunavir/rtv (600/100 mg b.i.d.) and a single dose of digoxin (0.4 mg) showed an increase of digoxin AUClast of 77% (ratio of Least Square Means (LSM) was 1.77 with a 90% CI of 0.90 to 3.50). It is recommended that the lowest dose of digoxin should initially be prescribed and digoxin dose should be titrated to obtain the desired clinical effect when co-administered with darunavir/rtv. Serum digoxin concentrations should be monitored to assist in the titration.

**Anticoagulants**
Warfarin concentrations may be affected when co-administered with darunavir/rtv. It is recommended that the international normalized ratio (INR) is monitored when warfarin is combined with darunavir/rtv.

**Anticonvulsants (phenobarbital, phenytoin and carbamazepine)**

*Phenobarbital and phenytoin*
Phenobarbital and phenytoin are inducers of CYP450 enzymes. Darunavir/rtv should not be used in combination with these medicines, as co-administration may cause significant decreases in darunavir plasma concentrations. This may result in loss of therapeutic effect to darunavir.

*Carbamazepine*
An interaction trial between darunavir/rtv (600/100 mg b.i.d.) and carbamazepine (200 mg b.i.d.) showed that the exposure to darunavir, co-administered with ritonavir, was unaffected by carbamazepine. Ritonavir exposure (AUC12h) was decreased by 49%. For carbamazepine, AUC12h was increased by 45%. No dose adjustment for darunavir/rtv is recommended. If there is a need to combine darunavir/rtv and carbamazepine, patients should be monitored for potential carbamazepine-related adverse events. Carbamazepine concentrations should be monitored and its dose should be titrated for adequate response. Based upon the findings, the carbamazepine dose may need to be reduced by 25% to 50% in the presence of darunavir/rtv.

**Colchicine**
Concomitant use of colchicine and darunavir/rtv may increase the exposure to colchicine. The following dose adjustments are recommended for colchicine. For the treatment of gout-flares in patients on darunavir/rtv, the recommended dose of colchicine is 0.6 mg (1 tablet), followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. For the prophylaxis of gout-flares in patients on darunavir/rtv, the recommended dose of colchicine is 0.3 mg q.d. or q.o.d. For the treatment of familial Mediterranean fever in patients on darunavir/rtv, the maximum dose of colchicine is 0.6 mg q.d. (may be given as 0.3 mg b.i.d.). Patients with renal or hepatic impairment should not be given colchicine with darunavir/rtv.

**Calcium channel blockers**
The exposure to calcium channel blockers (e.g., felodipine, nifedipine, nicardipine) may increase when darunavir/rtv are used concomitantly. Caution is warranted and careful clinical monitoring is recommended.

**Clarithromycin**
An interaction trial between darunavir/rtv (400/100 mg b.i.d.) and clarithromycin (500 mg b.i.d.)
showed an increase in exposure to clarithromycin by 57%, while exposure to darunavir was not affected. For patients with renal impairment, a dose reduction of clarithromycin should be considered.

**Dexamethasone**
Systemic dexamethasone induces CYP3A and thereby may decrease darunavir exposure. This may result in loss of therapeutic effect. Therefore this combination should be used with caution.

**Bosentan**
Concomitant use of bosentan and darunavir/rtv may increase plasma concentrations of bosentan. In patients who have been receiving darunavir/rtv for at least 10 days, start bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability. For patients on bosentan and initiating darunavir/rtv, discontinue the use of bosentan at least 36 hours prior to initiation of darunavir/rtv. After at least 10 days following the initiation of darunavir/rtv, resume bosentan at 62.5 mg q.d. or q.o.d. based upon individual tolerability.

**Fluticasone**
Concomitant use of inhaled fluticasone and darunavir/rtv may increase plasma concentrations of fluticasone. Alternatives should be considered, particularly for long term use.

**HMG-CoA reductase inhibitors**
HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, which are highly dependent on CYP3A metabolism, are therefore expected to have markedly increased plasma concentrations when co-administered with darunavir/rtv. Increased concentrations of HMG-CoA reductase inhibitors may cause myopathy, including rhabdomyolysis. Concomitant use of darunavir/rtv with lovastatin and simvastatin is therefore not recommended.
The results of an interaction trial with atorvastatin show that atorvastatin (10 mg q.d.) in combination with darunavir/rtv (300/100 mg b.i.d.) provides an exposure to atorvastatin, which is only 15% lower than that obtained with atorvastatin (40 mg q.d.) alone. When administration of atorvastatin and darunavir/rtv is desired, it is recommended to start with an atorvastatin dose of 10 mg q.d. A gradual dose increase of atorvastatin may be tailored to the clinical response.
darunavir/rtv (600/100 mg b.i.d.) increased exposure to a single dose of pravastatin (40 mg) by approximately 80%, but only in a subset of subjects. When administration of pravastatin and darunavir/rtv is required, it is recommended to start with the lowest possible dose of pravastatin and titrate up to the desired clinical effects while monitoring safety.
An interaction study evaluating darunavir/rtv (600/100 mg b.i.d.) in combination with rosuvastatin (10 mg q.d.) resulted in an increase in rosuvastatin exposure. It is recommended to start with the lowest possible dose of rosuvastatin and titrate up to the desired clinical effect while monitoring for safety.

**H2-Receptor antagonists and proton pump inhibitors**
Co-administration of omeprazole (20 mg q.d.) or ranitidine (150 mg b.i.d.) and darunavir/rtv (400/100 mg b.i.d.) did not affect the exposure to darunavir. Based on these results, darunavir/rtv can be co-administered with H2-receptor antagonists and proton pump inhibitors without dose adjustments.

**Inhaled beta agonist (salmeterol)**
Concomitant use of salmeterol and darunavir/rtv is not recommended. The combination may result in increased risk of cardiovascular adverse events with salmeterol, including QT prolongation, palpitations and sinus tachycardia.

**Immunosuppressants (cyclosporin, tacrolimus, sirolimus)**
Exposure to cyclosporine, tacrolimus, or sirolimus may be increased when co-administered with darunavir/rtv. Therapeutic drug monitoring of the immunosuppressive agent is recommended when co-administered with darunavir/rtv.

**Ketoconazole, itraconazole and voriconazole**
Ketoconazole, itraconazole and voriconazole are potent inhibitors as well as substrates of CYP3A. Concomitant systemic use of ketoconazole, itraconazole or voriconazole and darunavir/rtv may increase plasma concentrations of darunavir. Simultaneously, plasma concentrations of ketoconazole or itraconazole may be increased by darunavir/rtv. This was confirmed in an interaction trial where the concomitant administration of ketoconazole (200 mg b.i.d.) with darunavir/rtv (400/100 mg b.i.d.) increased exposure of ketoconazole and darunavir by 212% and 42%, respectively. When co-administration is required the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Plasma concentrations of voriconazole may be decreased in the presence of darunavir/ritonavir. Voriconazole should not be administered to patients receiving darunavir/rtv unless an assessment of the benefit/risk ratio justifies the use of voriconazole.

**Methadone**
An interaction trial investigating the effect of darunavir/rtv (600/100 mg b.i.d.) on a stable methadone maintenance therapy showed an AUC decrease of 16% for R-methadone. Based on pharmacokinetic and clinical findings, no adjustment of methadone dosage is required when initiating co-administration of darunavir/rtv. However, clinical monitoring is recommended as maintenance therapy may need to be adjusted in some patients.

**Buprenorphine/naloxone**
The results of an interaction trial with darunavir/rtv and buprenorphine/naloxone demonstrated that buprenorphine exposure was not affected when administered with darunavir/rtv. Exposure of the active metabolite, norbuprenorphine, increased by 46%. No dose adjustment for buprenorphine was required. Careful clinical monitoring is recommended if darunavir/rtv and buprenorphine are co-administered.

**Estrogen-based contraceptives**
The results of an interaction trial between darunavir/rtv (600/100 mg b.i.d.) and ethinylestradiol and norethindrone demonstrated that at steady-state systemic exposures to ethinylestradiol and norethindrone are decreased by 44% and 14%, respectively. Therefore, alternative methods of non-hormonal contraception are recommended.

**PDE-5 inhibitors**
*Treatment of erectile dysfunction*
In an interaction trial a comparable systemic exposure to sildenafil was observed for a single intake of 100 mg sildenafil alone and a single intake of 25 mg sildenafil co-administered with darunavir/rtv (400/100 mg b.i.d.). Concomitant use of PDE-5 inhibitors for the treatment of erectile dysfunction with darunavir/rtv should be done with caution. If concomitant use of darunavir/rtv with sildenafil, vardenafil, or tadalafil is indicated, sildenafil at a single dose not
exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours or
tadalafil at a single dose not exceeding 10 mg dose in 72 hours is recommended.

Treatment of pulmonary arterial hypertension

A safe and effective dose of sildenafil for the treatment of pulmonary arterial hypertension has not
been established. There is an increased potential for sildenafil-associated adverse events (including
visual disturbances, hypotension, prolonged erection and syncope). Therefore, co-administration of
darunavir/rtv with sildenafil when used for pulmonary arterial hypertension is contraindicated. For
the treatment of pulmonary arterial hypertension with tadalafil co-administered with
darunavir/rtv, a dose adjustment for tadalafil is warranted. In patients who have been receiving
darunavir/rtv for at least 1 week, start tadalafil at 20 mg q.d., and increase to 40 mg q.d. based upon
individual tolerability. For patients on tadalafil and initiating darunavir/rtv, discontinue the use of
tadalafil at least 24 hours prior to initiating darunavir/rtv and avoid the use of tadalafil during the
initiation of darunavir/rtv. After at least 1 week following the initiation of darunavir/rtv, resume
tadalafil at 20 mg q.d. and increase to 40 mg q.d. based upon individual tolerability.

Rifabutin

Rifabutin is a substrate of CYP450 enzymes. In an interaction trial, an increase of systemic exposure
to darunavir by 57% was observed, when darunavir/rtv (600/100 mg b.i.d.) was administered with
rifabutin (150 mg once every other day [q.o.d.]). Based on the safety profile of darunavir/rtv, the
increase in darunavir exposure in the presence of rifabutin does not warrant a dose adjustment for
darunavir/rtv. The interaction trial showed a comparable systemic exposure for rifabutin between
treatment at 300 mg q.d. alone and at 150 mg q.o.d. in combination with darunavir/rtv (600/100 mg
b.i.d.) with an increase in exposure to the active metabolite 25-O-desacetylrifabutin. A dosage
reduction of rifabutin by 75% of the usual dose of 300 mg/day (i.e. rifabutin 150 mg q.o.d.) and
increased monitoring for rifabutin-related adverse events is warranted in patients receiving the
combination.

Selective Serotonin Reuptake Inhibitors (SSRIs)

In an interaction trial between paroxetine (20 mg q.d.) or sertraline (50 mg q.d.) and darunavir/rtv
(400/100 mg b.i.d.), the exposure to darunavir was not affected by the presence of sertraline or
paroxetine. Exposure to sertraline and paroxetine, was decreased by 49% and 39%, respectively, in
the presence of darunavir/rtv. If SSRIs are co-administered with darunavir/rtv, the recommended
approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant
response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with
darunavir/rtv should be monitored for antidepressant response.
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