

# DARUNAVIR (DRV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Boosted DRV is listed as a potential third-line drug.<sup>6</sup>
- Indication: For treatment-experienced patients, such as those with HIV-1 strains resistant to more than one protease inhibitor (adults). It is also indicated in developed countries for treatment-naïve adult patients.<sup>83</sup>
- Originator company and product brand name: Tibotec (a subsidiary of Johnson & Johnson), Prezista.
- First approval by U.S. Food and Drug Administration (FDA): June 2006.<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.<sup>24</sup>
- World sales of originator product: More than US\$ 1 billion.<sup>84</sup>
- Patents: The basic patent was applied for by Searle and Monsanto in August 1993,<sup>85</sup> and is due to expire in 2013. Subsequently, NIH and the University of Illinois applied for patents more specifically related to darunavir in 1999<sup>86</sup> and licenced them to Tibotec for development.<sup>87</sup> Tibotec later applied for patents related to improved forms and combinations of darunavir.

## PRICE INFORMATION

### Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	Tibotec
Who can access this price?		See annex 2
DRV 300mg tablet	4*	1095 (0.750)

\*The dose of DRV must be boosted with RTV 100mg twice a day.

Continued overleaf ❖

## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations which for the first time call for the need of third-line therapy. Many studies are ongoing – drugs likely to have anti-HIV activity in third-line regimens are boosted darunavir (DRV), etravirine (ETV), and raltegravir (RAL).<sup>7</sup>

DRV, like all protease inhibitors (PIs) (with the exception of nelfinavir (NFV)), requires boosting with ritonavir (RTV). Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

Patient numbers in Africa for DRV are still small.

Tibotec (a subsidiary of Johnson & Johnson) signed a royalty-free, non-exclusive licence agreement with Aspen of South Africa in April 2007. This grants Aspen the right to register, package and distribute DRV in sub-Saharan Africa. In December 2008, Tibotec announced the signing of a similar agreement with Emcure to distribute DRV in India.<sup>88</sup> In 2011, Tibotec completed a second supply with Aspen covering the 300mg tablet but also the 600mg tablet. Aspen will distribute the medicine at \$1,095 per patient per year, and plans to replace the DRV 300mg tablet with the 600mg tablet, once it has been approved in most sub-Saharan Africa countries. Despite the VL, the price remains unaffordable for the developing world.

At the time of writing, the Aspen/Tibotec product is registered in at least eighteen countries with applications in process in four others. The price per patient per year will remain the same for both presentations.

These agreements exclude other low- and middle-income countries, for which the price paid in wealthy countries, at over \$13,100 per patient per year, is prohibitive.<sup>89</sup>

There is a need for generic manufacturers to supply a heat-stable DRV/r fixed-dose combination, which is currently not produced by the originator companies.

### Patents

The basic patents related to DRV<sup>90</sup> could not be applied for in India as the country did not grant patents on pharmaceuticals before 1995. Tibotec has nevertheless applied for several patents in India related to the pseudo-polymorphic form,<sup>91</sup> the method for preparation of key intermediates<sup>92</sup> of DRV and combinations of DRV with RTV<sup>93</sup> and with both TDF and RTV.<sup>94</sup> Some of these applications have been opposed by generic manufacturers.

The Indian patent office recently rejected several applications related to pseudo-polymorph,<sup>95</sup> the method for preparation of key intermediates and the combination of DRV with RTV.<sup>96</sup> The patent application on the combination of DRV with TDF was withdrawn after opposition.<sup>97</sup> The patent threat to the combination on DRV with RTV continues as Tibotec filed a divisional application<sup>98</sup> (still-pending) at the Indian patent office, along with appeals to the rejections.

In addition, Abbott has filed patent applications on RTV in India and other developing countries which, if granted, will block the development of and access to generic DRV/r fixed-dose combinations.

In China, Tibotec<sup>98</sup> was granted patents related to racemic and pseudo-polymorphic forms of DRV, methods for preparing intermediate compounds of DRV and use of DRV in combination with other ARVs.<sup>98</sup>

Similarly, more than 10 patent applications have been filed in Brazil, such as those related to the combination of DRV with TDF and RTV, as well as those related to the preparation of key intermediates and the pseudo-polymorphic form. In Brazil, DRV was included in the government's guidelines in 2008, but at \$6,037 per patient per year

(boosted with ritonavir), it is very expensive.

In September 2010, the U.S. National Institutes of Health (NIH) licensed a patent on darunavir to the Medicines Patent Pool,<sup>263</sup> a mechanism designed to boost access to more affordable AIDS drugs in the developing world, in a move that demonstrates political backing for the Medicines Patent Pool to benefit all developing countries. The NIH patent will not free the way for generic versions of darunavir, however, because additional patents are held by Tibotec.

### Paediatrics

In December 2008, DRV was approved for use in children between six and 18 years of age.<sup>23</sup> To simplify treatment for all children, there is an urgent need for studies on DRV to be completed in infants and children under six.

A paediatric 75mg tablet is available, but Tibotec has not provided price information for this product. There is no generic paediatric product yet available. The Tibotec product is however available on a compassionate use basis (free of charge) for sub-Saharan Africa and least-developed countries, until a pre-approval access programme is established with a local partner. The tablet is only suitable for children with the ability to swallow.

An added complexity is that DRV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of DRV in this population.

There is therefore a need for child-adapted formulations of DRV/r to be made more widely available. The Paediatric Antiretroviral Working Group of WHO considers the development of a fixed-dose combination containing darunavir and ritonavir to be a high priority, though it is still unclear what the ratio of the co-formulation will be.<sup>22</sup>