Informasi Produk untuk Pasien
EDURANT 25 mg tablet salut selaput
rilpivirine

Baca informasi ini secara lengkap dan seksama sebelum Anda mulai menggunakan obat ini karena informasi produk ini berisi informasi penting bagi Anda.
- Simpanlah informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker.
- Obat ini telah diresepkan untuk Anda saja. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka sama seperti Anda.
- Jika Anda mendapatkan efek samping, laporkan kepada dokter atau apoteker. Termasuk efek samping yang mungkin tidak tercantum dalam informasi produk ini. Lihat bagian 4.

Apa yang ada dalam informasi produk ini

1. Apakah EDURANT itu dan digunakan untuk apa
2. Apa saja yang perlu Anda ketahui sebelum Anda menggunakan EDURANT
3. Bagaimana cara menggunakan EDURANT
4. Efek samping yang mungkin terjadi
5. Bagaimana cara menyimpan EDURANT
6. Isi kemasan dan informasi lainnya

1. Apakah EDURANT itu dan digunakan untuk apa

EDURANT adalah obat yang digunakan untuk pengobatan infeksi Human Immunodeficiency Virus (HIV). Obat ini termasuk dalam kelompok obat HIV yang disebut non-nucleoside reverse transcriptase inhibitor (NNRTI). EDURANT bekerja dengan mengurangi jumlah HIV dalam tubuh Anda.

EDURANT digunakan dalam kombinasi dengan obat HIV lain untuk mengobati orang dewasa dan anak-anak usia 12 tahun dan lebih yang terinfeksi HIV dan yang belum pernah diobati sebelumnya dengan obat-obatan HIV.
Dokter anda akan menyarankan anda mengenai kombinasi obat yang terbaik bagi Anda.

2. Apa saja yang perlu Anda ketahui sebelum Anda menggunakan EDURANT

Jangan menggunakan EDURANT jika anda alergi terhadap rilpivirine atau salah satu bahan lain dari obat ini (tercantum dalam bagian 6).

Jangan menggunakan EDURANT dalam kombinasi dengan salah satu obat berikut karena dapat mempengaruhi cara kerja EDURANT atau obat lain tersebut :
- carbamazepine, oxcarbazepine, fenobarbital, fenitoin (obat-obatan untuk mengobati epilepsi dan mencegah kejang)
- rifampisin, rifapentin (obat-obatan untuk mengobati beberapa infeksi bakteri seperti tuberkulosis)
- omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, (inhibitor pompa proton yang merupakan obat mencegah dan mengobati sakit maag, mulas atau penyakit refluks asam)
- deksametason (kortikosteroid yang digunakan dalam beberapa kondisi seperti peradangan dan reaksi alergi) ketika diminum atau disuntikkan, kecuali digunakan sebagai pengobatan dosis tunggal
- Produk yang mengandung St John Wort (Hypericum perforatum) (produk herbal yang digunakan untuk depresi).

Jika anda menggunakan salah satu obat di atas, tanyakan kepada dokter Anda untuk alternatif lainnya.

Peringatan dan Perhatian
Bicaralah dengan dokter atau apoteker Anda sebelum menggunakan EDURANT.

EDURANT bukanlah obat untuk menyembuhkan infeksi HIV. Obat ini adalah bagian dari pengobatan untuk mengurangi jumlah virus dalam darah. Anda masih dapat menularkan HIV saat menggunakan obat ini, meskipun risikonya diturunkan melalui terapi antiretroviral yang efektif. Bicarakan dengan dokter anda mengenai tindakan pencegahan yang perlu dilakukan untuk menghindari penularan kepada orang lain.

Orang yang memakai EDURANT masih mungkin mengalami infeksi atau penyakit lain yang disebabkan oleh infeksi HIV. Anda harus tetap berkomunikasi secara rutin dengan dokter Anda.

EDURANT hanya digunakan dalam jumlah terbatas pada pasien berusia 65 tahun atau lebih. Jika Anda termasuk kelompok usia ini, silahkan tanyakan kepada dokter Anda mengenai penggunaan EDURANT.

Informasikan kepada dokter anda tentang situasi anda
Pastikan bahwa Anda memeriksa hal-hal berikut dan memberitahu dokter Anda jika salah satu dari hal berikut ini berlaku pada Anda.

- Informasikan kepada dokter anda jika anda menderita atau pernah mengalami masalah dengan liver anda, termasuk hepatitis B dan/atau C, dan/atau bermasalah dengan ginjal anda. Dokter anda akan mengevaluasi seberapa parah penyakit liver atau ginjal anda sebelum memutuskan apakah anda dapat menggunakan EDURANT.
- Informasikan kepada dokter Anda jika Anda melihat perubahan bentuk tubuh atau lemak. Peningkatan, penurunan atau redistribusi lemak tubuh dapat terjadi jika anda menggunakan EDURANT.
- Segera informasikan kepada dokter Anda jika Anda melihat gejala-gejala infeksi. Pada beberapa pasien dengan infeksi HIV lanjut dan riwayat infeksi oportunistik, tanda dan gejala peradangan dari infeksi sebelumnya dapat muncul segera setelah pengobatan HIV dimulai. Hal ini diyakini bahwa gejala-gejala tersebut disebabkan oleh peningkatan respon kekebalan tubuh, yang memungkinkan tubuh untuk melawan infeksi yang mungkin sudah ada tanpa gejala yang jelas.
- Selain infeksi oportunistik, gangguan autoimun (suatu kondisi yang terjadi dimana sistem kekebalan tubuh menyerang jaringan tubuh yang sehat) juga dapat terjadi setelah anda mulai menggunakan obat-obatan untuk pengobatan infeksi HIV anda. Gangguan autoimun dapat terjadi beberapa bulan setelah dimulainya pengobatan. Jika Anda melihat gejala-gejala infeksi atau gejala lain seperti kelemahan otot, kelemahan dimulai pada tangan dan kaki dan bergerak ke arah batang tubuh, palpitasi, tremor atau hiperaktif, silahkan segera beritahu dokter anda untuk mencari pengobatan yang diperlukan.
- Informasikan kepada dokter Anda, apabila Anda menggunakan obat-obatan yang menyebabkan jantung berdetak tidak teratur (Torsade de Pointes).

Anak-anak dan remaja
EDURANT tidak untuk digunakan pada anak-anak usia kurang dari 12 tahun, karena belum cukup studi untuk mempelajari pemakaian pada pasien tersebut.

Obat-obatan lain dan EDURANT
Anda harus menggunakan EDURANT bersama-sama dengan obat-obatan HIV lainnya. Dokter akan memberikan nasihat mengenai obat-obatan HIV lain yang dapat dikombinasikan dengan EDURANT dan anda bersama dengan dokter Anda dapat menentukan kombinasi terbaik yang sesuai dengan kebutuhan Anda. Ikuti instruksi dokter Anda dengan hati-hati.

Beberapa obat dapat mempengaruhi kadar EDURANT dalam darah ketika mereka dikonsumsi pada saat yang bersamaan dengan EDURANT.

Beritahu dokter atau apoteker anda jika anda menggunakan, atau mungkin akan menggunakan obat lain.

Tidak dianjurkan untuk mengkombinasikan penggunaan EDURANT dengan non-nucleoside reverse transcriptase inhibitor lain (NNRTI) seperti delavirdine, efavirenz, etravirine, dan nevirapine.

Efek EDURANT atau obat-obatan lain mungkin terpengaruh jika anda mengggunakan EDURANT bersama-sama dengan salah satu obat berikut. Informasikan kepada dokter Anda jika Anda menggunakan:

- rifabutin (obat untuk mengobati beberapa infeksi bakteri). Jika Anda minum obat ini saat menggunakan EDURANT, bacalah dengan seksama bagian 3 "Instruksi penggunaan yang tepat pada orang dewasa dan anak-anak (usia 12 hingga kurang dari 18 tahun)" mengenai bagaimana cara menggunakan EDURANT
- claritromisin, eritromisin (antibiotik)
- cimetidine, famotidine, nizatidine, ranitidine (antagonis reseptor H2 digunakan untuk mengobati lambung atau tukak usus atau digunakan untuk meringankan mulas karena refluks asam). Jika Anda minum obat ini saat menggunakan EDURANT, bacalah dengan seksama bagian 3 "Instruksi penggunaan yang tepat pada orang dewasa dan anak-anak (usia 12 hingga kurang dari 18 tahun)"
- Antasida (digunakan untuk mengobati penyakit yang berhubungan dengan asam lambung, misalnya, aluminium/magnesium hidroksida, kalsium karbonat). Jika Anda minum obat ini saat menggunakan EDURANT, bacalah dengan seksama bagian 3 "Instruksi penggunaan yang tepat pada orang dewasa dan anak-anak (usia 12 hingga kurang dari 18 tahun)"
- Metadon (digunakan untuk mengobati gejala putus narkotik (*withdrawal)* dan ketergantungan narkotika)
- dabigatran etexilate (antikoagulan).

EDURANT dengan makanan dan minuman
EDURANT **harus digunakan bersama dengan makanan**. Keberadaan makanan penting untuk mendapatkan kadar zat aktif yang tepat dalam tubuh anda. Minuman nutrisi (misalnya minuman kaya protein) saja tidak dapat menggantikan makanan. Lihat bagian 3 "Bagaimana cara menggunakan EDURANT".

Kehamilan dan menyusui
Segera beritahu dokter Anda jika anda sedang hamil atau berencana untuk hamil. Diskusikan dengan dokter Anda tentang penggunaan Edurant jika Anda sedang hamil.
Ibu yang terinfeksi HIV tidak boleh menyusui, karena ada kemungkinan menginfeksi bayi dengan HIV melalui ASI.

Tanyakan kepada dokter atau apoteker untuk mendapatkan saran sebelum menggunakan obat apapun.

Mengemudi dan menggunakan mesin
Beberapa pasien mungkin mengalami kelelahan, pusing atau mengantuk selama pengobatan dengan EDURANT. Jangan mengemudi atau mengoperasikan mesin jika Anda merasa lelah, pusing atau mengantuk saat menggunakan EDURANT.

EDURANT mengandung laktosa
Tablet EDURANT mengandung laktosa. Jika Anda diberitahu oleh dokter Anda bahwa Anda intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum menggunakan obat ini.

3. Bagaimana cara menggunakan EDURANT

Selalu minum obat ini sesuai dengan petunjuk dokter atau apoteker Anda. Tanyakan dengan dokter atau apoteker Anda jika anda tidak yakin.

Instruksi penggunaan yang tepat pada orang dewasa dan anak-anak (usia 12 hingga kurang dari 18 tahun)
Dosis EDURANT yang dianjurkan adalah satu tablet sekali sehari.

EDURANT harus digunakan bersamaan dengan makanan. Keberadaan makanan penting untuk mendapatkan kadar zat aktif yang tepat dalam tubuh Anda. Minuman nutrisi (misalnya minuman kaya protein) saja tidak dapat menggantikan makanan.

Berikut adalah tiga situasi yang memerlukan perhatian khusus:

1. **Jika Anda menggunakan rifabutin** (obat untuk mengobati beberapa infeksi bakteri), gunakan dua tablet EDURANT sekali sehari. Bila Anda berhenti minum rifabutin, gunakan satu tablet EDURANT sekali sehari. Bicaralah dengan dokter atau apoteker Anda jika anda tidak yakin.
2. **Jika anda menggunakan antasid** (obat untuk mengobati penyakit yang berhubungan dengan asam lambung seperti aluminium/magnesium hidroksida, kalsium karbonat). Gunakan antasida baik minimal 2 jam sebelum atau minimal 4 jam setelah EDURANT (lihat bagian 2 "Menggunakan obat-obatan lain").
3. **Jika Anda mengambil antagonis reseptor H2** (obat-obatan yang digunakan untuk mengobati lambung atau tukak usus atau digunakan untuk meringankan nyeri ulu hati karena refluks asam (seperti cimetidine, famotidine, nizatidine atau ranitidine). Gunakan antagonis reseptor H2 setidaknya 12 jam sebelum atau minimal 4 jam setelah EDURANT (lihat bagian 2 "Menggunakan obat-obatan lain"). Antagonis reseptor H2 tidak boleh digunakan dengan dosis dua kali sehari. Bicaralah dengan dokter Anda untuk dosis alternatif.

Membuka tutup *'Child Resistant'*

Botol plastik dilengkapi dengan tutup *'child resistant'*. Tutup dapat dibukan dengan menekan tutup yang beralur ke bawah sambil memutarnya berlawanan dengan arah jarum jam.

Jika Anda menggunakan EDURANT lebih dari dosis yang seharusnya
Segera hubungi dokter atau apoteker. Dalam kasus dosis berlebih (overdosis), Anda dapat menderita sakit kepala, mual, pusing, dan/atau mimpi abnormal.

Jika Anda lupa untuk menggunakan EDURANT
Jika Anda menyadarinya **dalam waktu 12 jam dari waktu dimana Anda biasanya menggunakan EDURANT**, maka Anda harus menggunakan tablet sesegera mungkin. EDURANT harus digunakan bersamaan dengan makanan. Kemudian gunakan dosis berikutnya seperti biasa. Jika Anda menyadarinya **setelah 12 jam**, maka lewatkan dosis itu dan gunakan dosis berikutnya seperti biasa. Jangan menggunakan dosis ganda untuk menggantikan dosis yang sudah terlewat.

Jika Anda muntah kurang dari 4 jam setelah minum EDURANT, minum tablet lain bersama dengan makanan. Jika Anda muntah lebih dari 4 jam setelah minum EDURANT, anda tidak perlu minum tablet lain sampai jadwal rutin tablet berikutnya.

Hubungi dokter jika tidak yakin tentang apa yang harus dilakukan jika Anda melewatkan dosis atau muntah.

Jangan berhenti menggunakan EDURANT
Jangan berhenti menggunakan EDURANT tanpa berbicara dengan dokter Anda terlebih dahulu. Walaupun Anda merasa lebih baik, jangan berhenti minum EDURANT atau obat HIV lainnya. Jika Anda melakukan hal tersebut maka akan meningkatkan risiko pengembangan resistensi virus Bicaralah dengan dokter Anda terlebih dahulu.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang sangat umum (terjadi pada lebih dari 1 dari 10 orang)
- peningkatan kolesterol dan/atau amilase pankreas dalam darah
- perubahan di salah satu tes liver rutin Anda (transaminase)
- sulit tidur (insomnia)
- sakit kepala, pusing
- mual

Efek samping yang umum (terjadi pada kurang dari 1 dari 10 orang)
- jumlah sel darah putih dan/atau jumlah trombosit rendah, penurunan hemoglobin dalam darah, peningkatan trigliserida, lipase dan / atau bilirubin dalam darah
- penurunan nafsu makan
- depresi, suasana hati tertekan
- mimpi abnormal, gangguan tidur
- mengantuk
- nyeri perut, muntah, lambung tak nyaman, mulut kering
- ruam
- kelelahan

Efek samping jarang (terjadi pada kurang dari 1 dalam 100 orang)
- tanda atau gejala peradangan atau infeksi (sindrom reaktivasi kekebalan tubuh).

Pelaporan efek samping
Jika anda mengalami efek samping, bicarakan dengan dokter atau apoteker. Ini termasuk efek samping yang mungkin tidak tercantum dalam informasi produk ini. Anda juga dapat melaporkan efek samping langsung dengan menghubungi drugsafety@jacid.jnj.com atau telfon (021) 2935 3935. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi lanjut tentang keamanan obat ini.

5. Bagaimana cara menyimpan EDURANT

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera pada karton dan botol setelah EXP. Tanggal kadaluwarsa mengacu pada hari terakhir dari bulan itu.

Simpan dalam botol aslinya untuk melindungi dari cahaya.

Jangan membuang obat-obatan melalui pembuangan limbah air atau limbah rumah tangga. Tanyakan pada apoteker Anda mengenai bagaimana membuang obat-obatan yang tidak Anda gunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apa isi EDURANT
- Zat aktif adalah rilpivirine dalam bentuk rilpivirine hidroklorida. Setiap tablet EDURANT mengandung rilpivirine hydrochloride setara dengan 25 mg rilpivirine.

- Bahan lain dari tablet inti dilapisi film adalah laktosa monohidrat, natrium croscarmellose, povidone K30, polisorbat 20, silisifikasi mikrokristalin selulosa dan magnesium stearat. Film-coating mengandung laktosa monohidrat, hipermelosa 2910 6 mPa.s, titanium dioksida E171, Polyethylene Glycol 3000 dan triasetin.

Seperti apa EDURANT dan isi kemasan
Tablet salut selaput berwarna putih sampai off-putih, bulat, cembung pada kedua sisi tablet, dengan "TMC" di satu sisi dan "25" di sisi lain. Satu botol plastik berisi 30 tablet salut selaput.

Harus dengan resep dokter

No. Reg: DKI1410901017A1

Pemilik Izin Edar
PT Soho Industri Pharmasi
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Dibuat oleh
Janssen-Cilag S.p.A., Latina, Italy

Based on SmPC Oct2015 + desk konsul 27Sep18

EDURANT™
rilpivirine hydrochloride

NAME OF THE MEDICINAL PRODUCT
EDURANT™ 25 mg film-coated tablets.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains rilpivirine hydrochloride equivalent to 25 mg rilpivirine.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
White to off-white, film-coated, round, biconvex, tablet of 6.4 mm, debossed with "TMC" on one side and "25" on the other side.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Antiviral for systemic use, NNRTI (non-nucleoside reverse transcriptase inhibitor), ATC code: J05AH05.

Mechanism of action
Rilpivirine is a diarylpyrimidine NNRTI of HIV-1, Rilpivirine activity is mediated by non-competitive inhibition of HIV-1 reverse transcriptase (RT). Rilpivirine does not inhibit the human cellular DNA polymerases α, β and γ.

Antiviral activity *in vitro*
Rilpivirine exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median EC_{50} value for HIV-1/IIIB of 0.73 nM (0.27 ng/ml). Although rilpivirine demonstrated limited *in vitro* activity against HIV-2 with EC_{50} values ranging from 2,510 to 10,830 nM (920 to 3,970 ng/ml), treatment of HIV-2 infection with EDURANT is not recommended in the absence of clinical data.

Rilpivirine also demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with EC_{50} values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/ml) and group O primary isolates with EC_{50} values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/ml).

Resistance
In cell culture
Rilpivirine-resistant strains were selected in cell culture starting from wild-type HIV-1 of different origins and subtypes as well as NNRTI resistant HIV-1. The most commonly observed resistance-associated mutations that emerged included L100I, K101E, V108I, E138K, V179F, Y181C, H221Y, F227C and M230I.

Resistance to rilpivirine was determined as a fold change in EC_{50} value (FC) above the biological cut-off (BCO) of the assay.

In treatment-naïve adult subjects
For the resistance analysis, a broader definition of virologic failure was used than in the primary efficacy analysis. In the week 48 pooled resistance analysis from the Phase III trials, 62 (of a total of 72) virologic failures in the EDURANT arm had resistance data at baseline and time of failure. In this analysis, the resistance-associated mutations (RAMs) associated with NNRTI resistance that developed in at least 2 rilpivirine virologic failure were: V90I, K101E, E138K, E138Q, V179I, Y181C, V189I, H221Y and F227C. In the trials, the presence of the mutations V90I and V189I, at baseline, did not affect response. The E138K substitution emerged most frequently during rilpivirine treatment, commonly in combination with the M184I substitution. In the week 48 analysis, 31 out of 62 of rilpivirine virologic failures had concomitant NNRTI and NRTI RAMs; 17 of those 31 had the combination of E138K and M184I. The most common mutations were the same in the week 48 and week 96 analyses.

In the week 96 pooled resistance analysis, lower rates of virologic failure were observed in the second 48 weeks than in the first 48 weeks of treatment. From the week 48 to the week 96 analysis, 24 (3.5%) and 14 (2.1%) additional virologic failures occurred in the EDURANT and efavirenz arm, respectively. Of these virologic failures, 9 out of 24 and 4 out of 14 were in subjects with a baseline viral load < 100,000 copies/ml, respectively.

Considering all of the available *in vitro* and *in vivo* data in treatment-naïve subjects, the following resistance-associated mutations, when present at baseline, may affect the activity of rilpivirine: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L. These rilpivirine resistance-associated mutations should only guide the use of EDURANT in the treatment-naïve population. These resistance-associated mutations were derived from *in vivo* data involving treatment-naïve subjects only and therefore cannot be used to predict the activity of rilpivirine in subjects who have virologically failed an antiretroviral-containing regimen.

As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT.

Cross-resistance

Site-directed NNRTI mutant virus

In a panel of 67 HIV-1 recombinant laboratory strains with once resistance-associated mutation at RT positions associated with NNRTI resistance, including the most commonly found K103N and Y181C, rilpivirine showed antiviral activity against 64 (96%) of these strains. The single resistance-associated mutation associated with a loss of susceptibility to rilpivirine were: K101P, Y181I and Y181V. The K103N substitution did not result in reduced susceptibility to rilpivirine by itself, but the combination of K103N and L100I resulted in a 7-fold reduced susceptibility to rilpivirine.

Recombinant clinical isolates

Rilpivirine retained sensitivity (FC ≤ BCO) against 62% of 4,786 HIV-1 recombinant clinical isolates resistant to efavirenz and/or nevirapine.

Treatment-naïve HIV-1 infected adult patients

In the week 96 pooled resistance analysis of the Phase III trials (ECHO and THRIVE), 42 out of 86 subjects with virologic failure on EDURANT showed treatment-emergent resistance to rilpivirine (genotypic analysis). In these patients, phenotypic cross-resistance to other NNRTIs was noted as follows: etravirine 32/42, efavirenz 30/42, and nevirapine 16/42. In patients with a baseline viral load ≤ 100,000 copies/ml, 9 out of 27 patients with virologic failure on EDURANT showed treatment-emergent resistance to rilpivirine (genotypic analysis), with the following frequency of phenotypic cross-resistance: etravirine 4/9, efavirenz 3/9, and nevirapine 1/9.

Effects on electrocardiogram

The effect of EDURANT at the recommended dose of 25 mg once daily on the QTcF interval was evaluated in a randomized, placebo and active (moxifloxacin 400 mg once daily) controlled crossover study in 60 healthy adults, with 13 measurements over 24 hours at steady-state. EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc.

When supratherapeutic doses of 75 mg once daily and 300 mg once daily of EDURANT were studied in healthy adults, the maximum mean time-matched (95% upper confidence bound) differences in QTcF interval from placebo after baseline correction were 10.7 (15.3) and 23.3 (28.4) ms, respectively. Steady-state administration of EDURANT 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 2.6-fold and 6.7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 25 mg once daily dose of EDURANT.

Clinical efficacy and safety

Treatment-naïve HIV-1 infected adult patients

The evidence of efficacy of EDURANT is based on the analyses of 96 week data from 2 randomised, double-blinded, active-controlled, Phase III trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE). The trials were identical in design, with the exception of the background regimen (BR). In the week 96 efficacy analysis, the virologic response rate [confirmed undetectable viral load (< 50 HIV-1 RNA copies/ml)] was evaluated in patients receiving EDURANT 25 mg once daily in addition to a BR versus patients receiving efavirenz 600 mg once daily in addition to a BR. Similar efficacy for EDURANT was seen in each trial demonstrating non-inferiority to efavirenz.

Antiretroviral treatment-naïve HIV-1 infected patients were enrolled who had a plasma HIV-1 RNA ≥ 5,000 copies/ml and were screended for susceptibility to N(t)RTIs and for absence of specific NNRTI resistance-associated mutations. In ECHO, the BR was fixed to the N(t)RTIs, tenofovir disoproxil fumarate plus emtricitabine. In THRIVE, the BR consisted of 2 investigator-selected N(t)RTIs: tenofovir disoproxil fumarate plus emtricibatine or zidovudine plus lamivudine or abacavir plus lamivudine. In ECHO, randomization was stratified by screening viral load. In THRIVE, randomization was stratified by screening viral load and by N(t)RTI BR.

This analysis included 690 patients in ECHO and 678 patients in THRIVE who had completed 96 weeks of treatment or discontinued earlier.

In the pooled analysis for ECHO and THRIVE, demographics and baseline characteristics were balanced between the EDURANT arm and the efavirenz arm. Table 1 displays selected baseline disease characteristics of the patients in the EDURANT and efavirenz arms.

Table 1: Baseline disease characteristics of antiretroviral treatment-naïve HIV-1 infected adult subjects in the ECHO and THRIVE trials (pooled analysis)

	Pooled data from the ECHO and THRIVE trials	
	EDURANT + BR N=686	**Efavirenz + BR N=682**
Baseline disease characteristics		
Median baseline plasma HIV-1 RNA (range), log_{10} copies/ml	5.0	5.0

	(2-7)	(3-7)
Median baseline CD4+ cell count (range), x 10^6 cells/l	249 (1-888)	260 (1-1137)
Percentage of subjects with: hepatitis B/C virus co-infection	7.3%	9.5%
Percentage of Patients with the following background regimens: tenofovir disoproxil fumarate plus emtricitabine zidovudine plus lamivudine abacavir plus lamivudine	 80.2% 14.7% 5.1%	 80.1% 15.1% 4.8%

BR=background regimen

Table 2 below shows the results of the week 48 and the week 96 efficacy analysis for patients treated with EDURANT and patients treated with efavirenz from the pooled data from the ECHO and THRIVE trials. The response rate (confirmed undetectable viral load < 50 HIV-1 RNA copies/ml) at week 96 was comparable between the EDURANT arm and the efavirenz arm. The incidence of virologic failure was higher in the EDURANT arm than the efavirenz arm at week 96; however, most of the virologic failures occurred within the first 48 weeks of treatment. Discontinuations due to adverse events were higher in the efavirenz arm at week 96 than the EDURANT arm. Most of these discontinuations occurred in the first 48 weeks of treatment.

Table 2: Virologic outcome in the ECHO and THRIVE trials (pooled data in the week 48 (primary) and week 96 analysis; ITT-TLOVR*)

	Outcome in the week 48 analysis			***Outcome in the week 96 analysis***		
	EDURANT + BR N=686	**Efavirenz + BR N=682**	**Observed difference (95% CI)±**	**EDURANT + BR N=686**	**Efavirenz + BR N=682**	**Observed difference (95% CI)±**
Response (confirmed < 50 HIV-1 RNA copies/ml)§#	84.3% (578/686)	82.3% (561/682)	2.0 (-2.0; 6.0)	77.6% (532/686)	77.6% (529/682)	0 (-4.4; 4.4)
Non-response Virologic failure †						
Overall	9.0% (62/686)	4.8% (33/682)	ND	11.5% (79/686)	5.9% (40/682)	ND
≤ 100,000	3.8% (14/368)	3.3% (11/330)	ND	5.7% (21/368)	3.6% (12/329)	ND
> 100,000	15.1% (48/318)	6.3% (22/352)	ND	18.2% (58/318)	7.9% (28/353)	ND
Death	0.1% (1/686)	0.4% (3/682)	ND	0.1% (1/686)	0.9% (6/682)	ND
Discontinued due to adverse event (AE)	2.0% (14/686)	6.7% (46/682)	ND	3.8% (48/682)	7.6% (52/682)	ND
Discontinued for non-AE reason ¶	4.5% (31/686)	5.7% (39/682)	ND	7.0% (48/682)	8.1% (55/682)	ND
Response by subcategory						
By background NRTI						
Tenofovir/emtricitabine	83.5% (459/550)	82.4% (450/546)	1.0 (-3.4; 5.5)	76.9% (423/550)	77.3% (422/546)	-0.4% (-5.4; 4.6)
Zidovudine/lamivudine	87.1% (88/101)	80.6% (83/103)	6.5 (-3.6; 16.7)	81.2% (82/101)	76.7% (79/103)	4.5% (-6.8; 15.7)
Abacavir/lamivudine	88.6% (31/35)	84.8% (28/33)	3.7 (-12.7; 20.1)	77.1% (27/35)	84.8% (28/33)	-7.7% (-26.7; 11.3)
By baseline viral load (copies/ml)						
≤ 100,000	90.2% (332/368)	83.6% (276/330)	6.6 (1.6; 11.5)	84.0% (309/368)	79.9% (263/329)	4.0 (-1.7; 9.7)
> 100,000	77.4% (246/318)	81.0% (285/352)	-3.6 (-9.8; 2.5)	70.1% (223/318)	75.4% (266/353)	-5.2 (-12.0; 1.5)
By baseline CD4 count (x 10^6 cells/l)						
< 50	58.8% (20/34)	80.6% (29/36)	-21.7 (-43.0; -0.5)	55.9% (19/34)	69.4% (25/36)	-13.6 (-36.4; 9.3)
≥ 50 - < 200	80.4% (156/194)	81.7% (143/175)	-1.3 (-9.3; 6.7)	71.1% (138/194)	74.9% (131/175)	-3.7 (-12.8; 5.4)
≥ 200 - < 350	86.9% (272/313)	82.4% (253/307)	4.5 (-1.2; 10.2)	80.5% (252/313)	79.5% (244/307)	1.0 (-5.3; 7.3)
≥ 350	90.3%	82.9%	7.4	85.4%	78.7%	6.8

	(130/144)	(136/164)	(-0.3; 15.0)	(123/144)	(129/164)	(-1.9; 15.4)

N = number of subjects per treatment group; ND = not determined.
* Intent-to-treat time to loss of virologic response
±Based on normal approximation
§Subjects achieved virologic response (two consecutive viral loads < 50 copies/ml) and maintained it through wee 48/96.
Predicted difference of response rates (95% CI) for the week 48 analysis: 1.6% (-2.2%; 5.3%) and for the week 96 analysis: -0.4% (-4.6%; 3.8%); both p-value < 0.0001 (non-inferiority at 12% margin) from logistic regression model, including stratification factors and study.
†Virologic failure in pooled efficacy analysis: includes subjects who were rebounder (confirmed viral load ≥ 50 copies/ml after being responder) or who were never suppressed (no confirmed viral load < 50 copies/ml, either ongoing or discontinued due to lack or loss of efficacy).
¶ e.g. lost to follow-up, non-compliance, withdrew consent.

At week 96, the mean change from baseline in CD4+ cell count was +228 x 10^6 cells/l in the EDURANT arm and +219 x 10^6 cells/l in the efavirenz arm in the pooled analysis of the ECHO and THRIVE trials [estimated treatment difference (95% CI): 11.3 (-6.8; 29.4)].

From the week 96 pooled resistance analysis, the resistance outcome for patients with protocol defined virological failure, and paired genotypes (baseline and failure) is shown in table 3.

Table 3: Resistance outcome by background NRTI regimen used (pooled data from the ECHO and THRIVE trials in the week 96 resistance analysis)

	tenofovir/ emtricitabine	zidovudine/ lamivudine	abacavir/ lamivudine	All*
EDURANT-treated				
Resistance# to emtricitabine/lamivudine % (n/N)	6.9 (38/550)	3.0 (3/101)	8.6 (3/35)	6.4 (44/686)
Resistance to rilpivirine % (n/N)	6.5 (36/550)	3.0 (3/101)	8.6 (3/35)	6.1 (42/686)
Efavirenz-treated				
Resistance to amtricitabine/lamivudine % (n/N)	1.1 (6/546)	1.9 (2/103)	3.0 (1/33)	1.3 (9/682)
Resistance to efavirenz % (n/N)	2.4 (13/546)	2.9 (3/103)	3.0 (1/33)	2.5 (17/682)

* The number of patients with virologic failure and paired genotypes (baseline and failure) were 71, 11, and 4 for EDURANT and 30, 10, and 2 for efavirenz, for the tenofovir/emtricitabine, zidovudine/lamivudine, and abacavir/lamivudine regimens, respectively.
# Resistance was defined as the emergence of any resistance-associated mutation at failure.

For those patients failing therapy with EDURANT and who developed resistance to EDURANT, cross-resistance to other approved NNRTIs (etravirine, efavirenz, nevirapine) was generally seen.

Study TMC278-C204 was a randomised, active-controlled, Phase IIb trial in antiretroviral treatment-naïve HIV-1 infected adult patients consisting of 2 parts: an initial partially blinded dose-finding part [(EDURANT) doses blinded] up to 96 weeks, followed by a long-term, open label part. In the open label part of the trial, patients originally randomised to one of the 3 doses of EDURANT were all treated with EDURANT 25 mg once daily in addition to a BR, once the dose for the phase III studies was selected. Patients in the control arm received efavirenz 600 mg once daily in addition to a BR in both parts of the study. The BR consisted of 2 investigator-selected N(t)RTIs: zidovudine plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine.

Study TMC278-C204 enrolled 368 HIV-1 infected treatment-naïve adult patients who had a plasma HIV-1 RNA ≥ 5000 copies/ml, previously received ≤ 2 weeks of treatment with an N(t)RTI or protease inhibitor, had no prior use of NNRTIs, and were screened for susceptibility to N(t)RTI and for absence of specific NNRTI resistance-associated mutations.

At 96 weeks, the proportion of patients with < 50 HIV-1 RNA copies/ml receiving EDURANT 25 mg (N=93) compared to patients receiving efavirenz (N=89) was 76% and 71%, respectively. The mean increase from baseline in CD4+ counts was 146 x 10^6 cells/l in patients receiving EDURANT 25 mg and 160 x 10^6 cells/l in patients receiving efavirenz.

Of those patients who were responders at week 96, 74% of patients remained with undetectable viral load (< 50 HIV-1 RNA copies/ml) at week 240 compared to 81% of patients receiving efavirenz. There were no safety concerns identified in the week 240 analyses.

Paediatric population

The pharmacokinetics, safety, tolerability and efficacy of EDURANT 25 mg once daily, in combination with an investigator-selected BR containing two NRTIs, was evaluated in trial TMC278-C213, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naive HIV-1 infected paediatric subjects 12 to less than 18 years of age and weighing at least 32 kg. This analysis included 36 patients who had completed at least 48 weeks of treatment or discontinued earlier.
The 36 subjects had a median age of 14.5 years (range: 12 to 17 years), and were 55.6% female, 88.9% Black and 11.1% Asian. The median baseline plasma HIV-1 RNA was 4.8 log10 copies per mL, and the median baseline CD4+ cell count was 414 x 10^6 cells/l (range: 25 to 983 x 10^6 cells/l).
The proportion of subjects with HIV-1 RNA < 50 copies/mL at week 48 (TLOVR) was 72.2% (26/36). The proportion of responders was higher in subjects with a baseline viral load ≤ 100,000 copies/mL (78.6%, 22/28) as compared to those with a baseline viral load > 100,000 copies/mL (50.0%, 4/8). The proportion of virological failures was 22.2% (8/36). The proportion of virologic failures was lower in subjects with a baseline viral load ≤ 100,000 copies/mL (17.9%, 5/28) as compared to those with a baseline viral load > 100,000 copies/mL (37.5%, 3/8). One subject discontinued due to an adverse event and 1 subject discontinued due to reasons other than an adverse event or virology failure. At week 48, the mean increase in CD4+ cell count from baseline was 201.2 x 10^6 cells/l.

Pregnancy
EDURANT in combination with a background regimen was evaluated in a clinical trial of 19 pregnant women during the second and third trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to EDURANT as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the 12 subjects that completed the study, 10 subjects were suppressed at the end of the study; in the other 2 subjects an increase in viral load was observed only postpartum, for at least 1 subject due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. EDURANT was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of EDURANT in HIV-1 infected adults (see Posology and method of administration; Special Warnings and Precautions for Use and Pharmacokinetic Properties).

Pharmacokinetic Properties
The pharmacokinetic properties of rilpivirine have been evaluated in adult healthy subjects and in adult-antiretroviral treatment-naïve HIV-1 infected patients 12 years of age and older. Exposure to rilpivirine was generally lower in HIV-1 infected patients than in healthy subjects.

Absorption
After oral administration, the maximum plasma concentration of rilpivirine is generally achieved within 4-5 hours. The absolute bioavailability of EDURANT is unknown.

Effect of food on absorption
The exposure to rilpivirine was approximately 40% lower when EDURANT was taken in a fasted condition as compared to a normal caloric meal (533 kcal) or high-fat high-caloric meal (928 kcal). When EDURANT was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a meal. EDURANT must be taken with a meal to obtain optimal absorption. Taking EDURANT in fasted condition or with only a nutritional drink may result in decreased plasma concentrations of rilpivirine, which could potentially reduce the therapeutic effect of EDURANT (see Polosogy and Method of Administration).

Distribution
Rilpivirine is approximately 99.7% bound to plasma proteins *in vitro*, primarily to albumin. The distribution of rilpivirine into compartments other than plasma (e.g., cerebrospinal fluid, genital tract secretions) has not been evaluated in humans.

Biotransformation
In vitro experiments indicate that rilpivirine primarily undergoes oxidative metabolism mediated by the cytochrome P450 (CYP) 3A system.

Elimination
The terminal elimination half-life of rilpivirine is approximately 45 hours. After single dose oral administration of ^{14}C-rilpivirine, on average 85% and 6.1% of the radioactivity could be retrieved in faeces and urine, respectively. In faeces, unchanged rilpivirine accounted for on average 25% of the administered dose. Only trace amounts of unchanged rilpivirine (< 1% of dose) were detected in urine.

Additional information on special populations
Paediatric population (17 years of age and younger)
The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1 infected paediatric subjects 12 to less than 18 years of age receiving EDURANT 25 mg once daily were comparable to those in treatment-naive HIV-1 infected adults receiving EDURANT 25 mg once daily. There was no impact of body weight on rilpivirine pharmacokinetics in paediatric subjects in trial C213 (33 to 93 kg), similar to what was observed in adults.

The pharmacokinetics of rilpivirine in paediatric patients less than 12 years of age are under investigation. Dosing recommendations for paediatric patients less than 12 years of age cannot be made due to insufficient data (see Posology and Method of Administration).

Older people
Population pharmacokinetic analysis in HIV infected patients showed that rilpivirine pharmacokinetics are not different across the age range (18 to 78 years) evaluated, with only 3 subjects aged 65 years or older. No dose adjustment of EDURANT is required in elderly patients. EDURANT should be used with caution in this population (see Posology and Method of Administration).

Gender
No clinically relevant differences in the pharmacokinetics of rilpivirine have been observed between men and women.

Race
Population pharmacokinetic analysis of rilpivirine in HIV infected patients indicated that race had no clinically relevant effect on the exposure to rilpivirine.

Hepatic impairment
Rilpivirine is primarily metabolised and eliminated by the liver. In a study comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of rilpivirine was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment.

No dose adjustment is suggested but caution is advised in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see Posology and Method of Administration).

Hepatitis B and/or hepatitis C virus co-infection
Population pharmacokinetic analysis indicated that hepatitis B and/or C virus co-infection had no clinically relevant effect on the exposure to rilpivirine.

Renal impairment
The pharmacokinetics of rilpivirine have not been studied in patients with renal insufficiency. Renal elimination of rilpivirine is negligible. No dose adjustment is needed for patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution, as plasma concentrations may be increased due to alteration of drug absorption, distribution and/or metabolism secondary to renal dysfunction. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor should only be used if the benefit outweighs the risk. As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis (see Posology and Method of Administration).

Pregnancy and Postpartum
The exposure to total rilpivirine after intake of rilpivirine 25 mg once daily as part of an antiretroviral regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum (see table 4). The decrease in unbound (ie, active) rilpivirine pharmacokinetic parameters during pregnancy compared to postpartum was less pronounced than for total rilpivirine.

In women receiving rilpivirine 25 mg once daily during the 2nd trimester of pregnancy, mean intra-individual values for total rilpivirine C_{max}, AUC_{24h} and C_{min} values were, respectively, 21%, 29% and 35% lower as compared to postpartum; during the 3rd trimester of pregnancy, C_{max}, AUC_{24h} and C_{min} values were, respectively, 20%, 31% and 42% lower as compared to postpartum.

Table 4: Pharmacokinetic Results of Total Rilpivirine After Administration of Rilpivirine 25 mg Once Daily as Part of an Antiretroviral Regimen, During the 2nd Trimester of Pregnancy, the 3rd Trimester

Pharmacokinetics of total rilpivirine (mean ± SD, t_{max}: median [range])	**Postpartum (6-12 Weeks) (n=11)**	**2nd Trimester of pregnancy (n=15)**	**3rd Trimester of pregnancy (n=13)**
C_{min}, ng/mL	84.0 ± 58.8	54.3 ± 25.8	52.9 ± 24.4
C_{max}, ng/mL	167 ± 101	121 ± 45.9	123 ± 47.5
t_{max}, h	4.00 (2.03-25.08)	4.00 (1.00-9.00)	4.00 (2.00-24.93)
AUC_{24h}, ng.h/mL	2714 ± 1535	1792 ± 711	1762 ± 662

Preclinical Safety Data

Repeated dose toxicity

Liver toxicity associated with liver enzyme induction was observed in rodents. In dogs, cholestasis-like effects were noted.

Reproductive toxicology studies

Studies in animals have shown no evidence of relevant embryonic or foetal toxicity or an effect on reproductive function. There was no teratogenicity with rilpivirine in rats and rabbits. The exposures at the embryo-foetal No Observed Adverse Effects Levels (NOAELs) in rats and rabbits were respectivetly 15 and 70 times higher than the exposure in humans at the recomemnded dose of 25 mg once daily.

Carcinogenesis and mutagenesis

Rilpivirine was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 104 weeks. At the lowest tested doses in the carcinogenicity studies, the systemic exposures (based on AUC) to rilpivirine were 21-fold (mice) and 3-fold (rats), relative to those observed in humans at the recommended dose (25 mg once daily). In rats, there were no drug-related neoplasms. In mice, rilpivirine was positive for hepatocellular neoplasms in both males and females. The observed hepatocellular findings in mice may be rodent-specific.

Rilpivirine has tested negative in the absence and presence of a metabolic activation system in the *in vitro* Ames reverse mutation assay and the *in vitro* clastogenicity mouse lymphoma assay. Rilpivirine did not induce chromosomal damage in the *in vivo* micronucleus test in mice.

CLINICAL PARTICULARS

Therapeutic Indications

EDURANT, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/ml.

The indication in adults is based on week 96 safety and efficacy analysis two randomised, double-blind, controlled, Phase III trials treatment-naïve patients and in paediatric patients (12 to less than 18 years of age is based on week 48 safety and efficacy analysis from Phase IIb trial in treatment-naïve patients.
As with other antiretroviral medicinal products, genotypic resistance testing should guide the use of EDURANT.

Posology and method of administration

Therapy should be initiated by a physician experienced in the management of HIV infection.

Posology

EDURANT must always be given in combination with other antiretroviral medicinal products.

Adults and paediatric patients (12 to less than 18 years of age)

The recommended dose of EDURANT is one 25 mg tablet taken once daily. EDURANT **must be taken with a meal** (see *Pharmacokinetic Properties*).

Dose adjustment

For patients concomitantly receiving rifabutin, the EDURANT dose should be increased to 50 mg (two tablets of 25 mg each) taken once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily (see *Interaction with other medicinal products and other forms of interaction*)

Missed dose

If the patient misses a dose of EDURANT within 12 hours of the time it is usually taken, the patient must take EDURANT with a meal as soon as possible and resume the normal dosing schedule. If a patient misses a dose of EDURANT by more than 12 hours, the patient should not take the missed dose, but resume the usual dosing schedule.

If a patient vomits with 4 hours of taking EDURANT, another EDURANT tablet should be taken with a meal. If a patient vomits more than 4 hours after taking EDURANT, the patient does not need to take another dose of EDURANT until the next regularly scheduled dose.

Special populations

Older people

There is limited information regarding the use of EDURANT in patients > 65 years of age. No dose adjustment of EDURANT is required in elderly patients (see *Pharmacokinetic Properties*). EDURANT should be used with caution in this population.

Paediatric population

The safety and efficacy of EDURANT in children aged < 12 years have not yet been established. No data are available

Hepatic impairment
There is limited information regarding the use of EDURANT in patients with mild or moderately hepatic impairment (Child-Pugh score A or B). No dose adjustment of EDURANT is required in patients with mild or moderate hepatic impairment. EDURANT should be used with caution in patients with moderate hepatic impairment. EDURANT has not been studied in patients with severe hepatic impairment (Child-Pugh score C). Therefore, EDURANT is not recommended in patients with severe hepatic impairment (see *Pharmacokinetic Properties*).

Renal impairment
EDURANT has mainly been studied in patients with normal renal function. No dose adjustment of EDURANT is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, EDURANT should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of EDURANT with a strong CYP3A inhibitor (e.g., ritonavir-boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk (see *Pharmacokinetic Properties*).

Treatment with EDURANT resulted in an early small increase of mean serum creatinine levels which remained stable over time and is not considered clinically relevant (see *Undesirable Effects*).

Pregnancy
Lower exposures of EDURANT were observed during pregnancy, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered (see *Special Warnings and Precautions for Use; Fertility, pregnancy and lactation; Pharmacodynamic Properties* and *Pharmacokinetic Properties*).

Method of administration
EDURANT must be taken orally, once daily **with a meal** (see *Pharmacokinetic Properties*). It is recommended that the EDURANT film-coated tablet be swallowed whole with water and not be chewed or crushed.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in List of excipients.

EDURANT should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of EDURANT (see *Interaction with other medicinal products and other forms of interaction*):
- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*)

Special Warnings and Precautions for Use
Patients should be advised that current antiretroviral therapy does not cure HIV, and there is still a risk of passing HIV to others through sexual contact or contamination with blood when taking EDURANT. Appropriate precautions to prevent the transmission of HIV should continue to be employed.

Virologic failure and development of resistance
EDURANT has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy. The list of rilpivirine resistance-associated mutations presented in *Pharmacodynamic Properties* should only guide the use of EDURANT in the treatment-naïve population.

In the pooled efficacy analysis from the Phase III trials in adults through 96 weeks, patients treated with EDURANT with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virology failure (18.2% with EDURANT versus 7.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (5.7% with EDURANT versus 3.6% with efavirenz). The greater risk of virologic failure for patients in the EDURANT arm was observed in the first 48 weeks of these trials (see *Pharmacodynamic Properties*). Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment-emergent resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on EDURANT than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance (see *Pharmacodynamic Properties*).

No new information was identified in paediatric patients 12 to less than 18 years of age in trial C213.

As with other antiretroviral medicinal products, resistance testing should guide the use of EDURANT (see *Pharmacodynamic Properties*).

Cardiovascular

At supra-therapeutic dose (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG) (see *Interaction with other medicinal products and other forms of interaction*; *Undesirable Effects* and *Pharmacokinetic Properties*). EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. EDURANT should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Fat redistribution
Combination antiretroviral therapy (CART) has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients. The long- term consequences of these events are currently unknown. Knowledge about the mechanism is incomplete. A connection between visceral lipomatosis and protease inhibitors (PIs) and lipoatrophy and nucleoside reverse transcriptase inhibitors (NRTIs) has been hypothesised. A higher risk of lipodystrophy has been associated with individual factors such as older age and with drug-related factors such as longer duration of antiretroviral treatment and associated metabolic disturbance. Clinical examination should include evaluation for physical signs of fat redistribution (see *Undesirable Effects*)

Immune reactivation syndrome
In HIV infected patients with severe immune deficiency at the time of institution of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

Autoimmune disorders (such as Graves' disease) have also reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see *Undesirable Effects*).

Pregnancy
EDURANT should be used during pregnancy only if the potential benefit justifies the potential risk. Lower exposures of EDURANT were observed when EDURANT 25 mg once daily was taken during pregnancy. In the phase 3 studies, lower EDURANT exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely (see *Fertility, pregnancy and lactation; Pharmacodynamic Properties* and *Pharmacokinetic Properties*). Alternatively, switching to another ART regimen could be considered.

Important information about some of the ingredient of EDURANT
EDURANT contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Interaction with other medicinal products and other forms of interaction
Medicinal products that affect rilpivirine exposure
Rilpivirine is primarily metabolized by cytochrome P450 (CYP)3A. Medicinal products that induce or inhibit CYP3A may thus affect the clearance of rilpivirine (see *Pharmacokinetic Properties).* Co-administration of EDURANT and medicinal products that induce CYP3A has been observed to decrease the plasma concentrations of rilpivirine, which could reduce the therapeutic effect of EDURANT. Co-administration of EDURANT and medicinal products that inhibit CYP3A has been observed to increase the plasma concentrations of rilpivirine.
Co-administration of EDURANT with medicinal products that increase gastric pH may result in decreased plasma concentrations of rilpivirine which could potentially reduce the therapeutic effect of EDURANT.

Medicinal products that are affected by the use of rilpivirine
EDURANT at a dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes.
Rilpivirine inhibits P-glycoprotein *in vitro* (IC_{50} is 9.2 µM). In a clinical study rilpivirine did not significantly affect the pharmacokinetics of digoxin. However, it may not be completely excluded that rilpivirine can increase the exposure to other drugs transported by P-glycoprotein that are more sensitive to intestinal P-gp inhibition, e.g. dabigatran etexilate.

Rilpivirine is an *in vitro* inhibitor of the transporter MATE-2K with an IC50 of < 2.7 nM. The clinical implications of this finding are currently unknown.

Established and theoretical interaction with selected antiretrovirals and non-antiretroviral medicinal products are listed in table 5.

Interaction table
Interaction studies have only been performed in adults.
Interactions between rilpivirine and co-administered medicinal products are listed in table 5 (increase in indicated as "↑", decrease as "↓", no change as "↔", not applicable as "NA", confidence interval as "CI").

Table 5: INTERACTIONS AND DOSE RECOMMENDATIONS WITH OTHER MEDICINAL PRODUCTS		
Medicinal products by therapeutic areas	**Interaction Geometric mean change (%)**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
Antiretrovirals		
HIV NRTIs/N[t]RTIs		
Didanosine*# 400 mg once daily	didanosine AUC↑ 12% didanosine C_{min} NA didanosine C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required. Didanosine should be administered at least two hours before or at least four hours after EDURANT.
Tenofovir disoproxil fumarate *# 300 mg once daily	tenofovir AUC↑ 23% tenofovir C_{min} ↑ 24% tenofovir C_{max} ↑ 19% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Other NRTIs (abacavir, emtricitabine, lamivudine, stavudine and zidovudine)	Not studied. No clinically relevant drug-drug interactions are expected.	No dose adjustment is required.
HIV NNRTIs		
NNRTIs (delavirdine, efavirenz, etravirine, nevirapine)	Not studied.	It is not recommended to co-administer EDURANT with other NNRTIs.
HIV PIs – with co-administration of low dose ritonavir		
Darunavir/ritonavir *# 800/100 mg once daily	darunavir AUC ↔ darunavir C_{min} ↓ 11% darunavir C_{max} ↔ rilpivirine AUC ↑ 130% rilpivirine C_{min} ↑ 178% rilpivirine C_{max} ↑ 79% (inhibition of CYP3A enzymes)	Concomitant use of EDURANT with ritonavir-boosted PIs causes an increased in the plasma concentrations of rilpivirine, but no dose adjustment is required.
Lopinavir/ritonavir (soft gel capsule) *# 400/100 mg twice daily	lopinavir AUC ↔ lopinavir C_{min} ↓ 11% lopinavir C_{max} ↔ rilpivirine AUC ↑ 52% rilpivirine C_{min} ↑ 74% rilpivirine C_{max} ↑ 29% (inhibition of CYP3A enzymes)	
Other boosted PIs (atazanavir/ritonavir, fosamprenavir/ritonavir, saquinavir/ritonavir, tipranavir/ritonavir)	Not studied.	
HIV PIs – without co-administration of low dose ritonavir		
Unboosted PIs (atazanir, fosamprenavir, indinavir, nelfinavir)	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	No dose adjustment is required.
CCR5 Antagonists		
Maraviroc	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
HIV Integrase Strand Transfer Inhibitors		
Raltegravir*	raltegravir AUC ↑ 9% raltegravir C_{min} ↑ 27% raltegravir C_{max} ↑ 10% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Other Antiviral Agents		

Ribavirin	Not studied. No clinically relevant drug-drug interaction is expected.	No dose adjustment is required.
Simeprevir*	simeprevir AUC ↔ simeprevir C_{min} ↔ simeprevir C_{max} ↑ 10% rilpivirine AUC ↔ rilpivirine C_{min} ↑ 25% rilpivirine C_{max} ↔	No dose adjustment is required.
OTHER AGENTS		
ANTICONVULSANTS		
Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	EDURANT must not be used in combination with these anticonvulsants as co-administration may result in loss of therapeutic effect of EDURANT.
AZOLE ANTIFUNGAL AGENTS		
Ketoconazole *# 400 mg once daily	ketoconazole AUC ↓ 24% telaprevir C_{min} ↓ 66% telaprevir C_{max} ↔ (induction of CYP3A due to high rilpivirine dose in the study) rilpivirine AUC ↑ 49% rilpivirine C_{min} ↑ 79% rilpivirine C_{max} ↑ 30% (inhibition of CYP3A enzymes)	At the recommended dose of 25 mg once daily, no dose adjustment is required when EDURANT is co-administered with ketoconazole.
Fluconazole Itraconazole Posaconazole Voriconazole	Not studied. Concomitant use of EDURANT with azole antifungal agents may cause an increase in the plasma concentrations of rilpivirine. (inhibition of CYP3A enzymes)	No dose adjustment is required.
ANTIMYCOBACTERIALS		
Rifabutin * 300 mg once daily † 300 mg once daily (+ 25 mg once daily rilpivirine) 300 mg once daily (+ 50 mg once daily rilpivirine)	rifabutin AUC ↔ rifabutin C_{min} ↔ rifabutin C_{max} ↔ 25-*O*-desacetyl-rifabutin AUC ↔ 25-*O*-desacetyl-rifabutin C_{min} ↔ 25-*O*-desacetyl-rifabutin C_{max} ↔ rilpivirine AUC ↓ 42% rilpivirine C_{min} ↓ 48% rilpivirine C_{max} ↓ 31% rilpivirine AUC ↑ 16% * rilpivirine C_{min} ↔ * rilpivirine C_{max} ↑ 43% * * compared to 25 mg once daily rilpivirine alone (induction of CYP3A enzymes)	Throughout co-administration of EDURANT with rifabutin, the EDURANT dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the EDURANT dose should be decreased to 25 mg once daily.
Rifampicin *# 600 mg once daily	rifampicin AUC ↔ rifampicin C_{min} NA rifampicin C_{max} ↔ 25-desacetyl-rifampicin AUC ↓9% 25-desacetyl-rifampicin C_{min} NA 25-desacetyl-rifampicin C_{max} ↔ rilpivirine AUC ↓ 80% rilpivirine C_{min} ↓ 89% rilpivirine C_{max} ↓ 69%	EDURANT must not be used in combination with rifampicin as co-administration is likely to result in loss of therapeutic effect of EDURANT.

	(induction of CYP3A enzymes)	
Rifapentine	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	EDURANT must not be used in combination with rifapentine as co-administration is likely to result in loss of therapeutic effect of EDURANT.
MACROLIDE ANTIBIOTICS		
Clarithromycin Erythromycin	Not studied. Increased exposure of rilpivirine is expected. (inhibition of CYP3A enzymes)	Where possible, alternatives such as azithromycin should be considered.
GLUCOCORTICOIDS		
Dexamethasone (systemic, except for single dose use)	Not studied. Dose dependent decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	EDURANT should not be used in combination with systemic dexamethasone (except as a single dose) as co-administration may result in loss of therapeutic effect of EDURANT. Alternatives should be considered, particularly for long-term use.
PROTON PUMP INHIBITIONS		
Omeprazole *# 20 mg once daily	omeprazole AUC ↓ 14% omeprazole C_{min} NA omeprazole C_{max} ↓ 14% rilpivirine AUC ↓ 40% rilpivirine C_{min} ↓ 33% rilpivirine C_{max} ↓ 40% (reduced absorption due to gastric pH increase)	EDURANT must not be used in combination with proton pump inhibitors as co-administration is likely to result in loss of therapeutic effect of EDURANT.
Lansoprazole Rabeprazole Pantoprazole Esomeprazole	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (reduced absorption due to gastric pH increase)	
H_2-RECEPTOR ANTAGONISTS		
Famotidine *# 40 mg single dose taken 12 hours before rilpivirine	rilpivirine AUC ↓ 9% rilpivirine C_{min} NA rilpivirine C_{max} ↔	The combination of EDURANT and H_2-receptor antagonists should be used with particular caution. Only H_2-receptor antagonists that can be dosed once daily should be used. A strict dosing schedule, with intake of H_2-receptor antagonists at least 12 hours before or at least 4 hours after EDURANT should be used.
Famotidine *# 40 mg single dose taken 2 hours before rilpivirine	rilpivirine AUC ↓ 76% rilpivirine C_{min} NA rilpivirine C_{max} ↓ 85% (reduced absorption due to gastric pH increase)	
Famotidine *# 40 mg single dose taken 4 hours after rilpivirine	rilpivirine AUC ↑ 13% rilpivirine C_{min} NA rilpivirine C_{max} ↑ 21%	
Cimetidine Nizatidine Ranitidine	Not studied. (reduced absorption due to gastric pH increase)	
ANTACIDS		
Antacids (e.g., aluminium or magnesium hydroxide, calcium carbonate)	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (reduced absorption due to gastric pH increase)	The combination of EDURANT and antacids should be used with particular caution. Antacids should only be administered either at least 2 hours before or at least 4 hours after EDURANT.
NARCOTIC ANALGESICS		
Methadone * 60-100 mg once daily, individualized dose	R(-) methadone AUC ↓ 16% R(-) methadone C_{min} ↓ 22% R(-) methadone C_{max} ↓ 14%	No dose adjustments are required when initiating co-administration of methadone with EDURANT.

	rilpivirine AUC ↔ * rilpivirine C_{min} ↔ * rilpivirine C_{max} ↔ * * based on historic controls	However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
ANTIARRHYTHMICS		
Digoxin *	digoxin AUC ↔ digoxin C_{min} NA digoxin C_{max} ↔	No dose adjustment is required.
ANTICOAGULANTS		
Dabigatran etexilate	Not studied. A risk for increases in dabigatran plasma concentrations cannot be excluded. (inhibition of intestinal P-gp)	The combination of EDURANT and dabigatran etexilate should be used with caution.
ANTIDIABETICS		
Metformin* 850 mg single dose	metformin AUC ↔ metformin C_{min} NA metformin C_{max} ↔	No dose adjustment required
HERBAL PRODUCTS		
St John's wort *(Hypericum perforatum)*	Not studied. Significant decreases in rilpivirine plasma concentrations are expected. (induction of CYP3A enzymes)	EDURANT must not be used in combination with products containing St John's wort as co-administration may result to loss of therapeutic effect of EDURANT.
ANALGESICS		
Paracetamol *# 500 mg single dose	paracetamol AUC ↔ paracetamol C_{min} NA paracetamol C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↑ 26% rilpivirine C_{max} ↔	No dose adjustment is required.
ORAL CONTRACEPTIVES		
Ethynilestradiol * 0.035 mg once daily Norethindrone * 1 mg once daily	ethynilestradiol AUC ↔ ethynilestradiol C_{min} ↔ ethynilestradiol C_{max} ↑ 17% norethindrone AUC ↔ norethindrone C_{min} ↔ norethindrone C_{max} ↔ rilpivirine AUC ↔ * rilpivirine C_{min} ↔ * rilpivirine C_{max} ↔ * * based on historic controls	No dose adjustment is required.
HMG CO-A REDUCTASE INHIBITORS		
Atorvastatin *# 40 mg once daily	atorvastatin AUC ↔ atorvastatin C_{min} ↓ 15% atorvastatin C_{max} ↑ 35% rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↓ 9%	No dose adjustment is required.
PHOSPHODIESTERASE TYPE 5 (PDE-5) INHIBITORS		
Sildenafil *# 50 mg single dose	sildenafil AUC ↔ sildenafil C_{min} NA sildenafil C_{max} ↔ rilpivirine AUC ↔ rilpivirine C_{min} ↔ rilpivirine C_{max} ↔	No dose adjustment is required.
Vardenafil Tadalafil	Not studied.	No dose adjustment is required.

* The interaction between EDURANT and the medicinal product was evaluated in a clinical study. All other drug-drug interactions shown are predicted.

This interaction study has been performed with a dose higher than the recommended dose for EDURANT assessing the maximal effect on the co-administered medicinal product. The dosing recommendation is applicable to the recommended dose of EDURANT of 25 mg once daily.

† This interaction study has been performed with a dose higher than the recommended dose for EDURANT.

QT prolonging medicinal products
There is limited information available on the potential for a pharmacodynamic interaction between rilpivirine and medicinal products that prolong the QTc interval of the ECG. In a study of healthy subjects, supratherapeutic doses of rilpivirine (75 mg once daily and 300 mg once daily) have been shown to prolong the QTc interval of the ECG (see Pharmacodynamic Properties). EDURANT should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes.

Fertility, pregnancy and lactation
Pregnancy
There are limited amount of data (less than 300 pregnancy outcomes) from the use of EDURANT in pregnant women (see Special Warnings and Precautions for Use; Pharmacodynamic Properties and Pharmacokinetic Properties). Lower exposures of EDURANT were observed during pregnancy, therefore viral load should be monitored closely.

Studies in animals have shown no reproductive toxicity (see Preclinical Safety Data) and limited placenta passage. It is not known whether placental transfer of EDURANT occurs in pregnant women. There was no teratogenicity with rilpivirine in rats and rabbits.

EDURANT should not be used during pregnancy unless clearly needed.

Breast-feeding
It is not known whether rilpivirine is excreted in human milk. EDURANT is excreted in the milk of rats. Because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants, mothers should be instructed not to breast-feed if they are receiving EDURANT.

Fertility
No human data on the effect of rilpivirine on fertility are available. No clinically relevant effects on fertility were seen in animal studies (see Preclinical Safety Data).

Effects on ability to drive and use machines
EDURANT has no or negligible influence on the ability to drive and use machines. No studies on the effects of EDURANT on the ability to drive and use machines have been performed. Fatigue, dizziness and somnolence have been reported in some patients taking EDURANT and should be considered when assessing a patient's ability to drive or operate machinery.

UNDESIRABLE EFFECTS
Summary of the safety profile

The safety assessment is based on the week 96 pooled data from 1,368 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE) in antiretroviral treatment-naïve HIV-1 infected adult patients, 686 of whom received EDURANT (25 mg once daily) (see Pharmacodynamic Properties). The median duration of exposure for patients in the EDURANT arm and efavirenz arm was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment.

Tabulated summary of adverse reactions
ADRs reported in adult patients treated with EDURANT are summarized in table 6. Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, are included in a footnote to table 2. The ADRs are listed by system organ class (SOC) and frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, ADRs are presented in order of decreasing frequency.

Table 6: ADRs reported in antiretroviral treatment-naïve HIV-1 infected adult patients treated with EDURANT (pooled data from the week 96 analysis of the Phase III ECHO and THRIVE trials) N = 686

System Organ Class (SOC)	**Frequency Category**	**ADRs (EDURANT + BR)**
Blood and lymphatic system disorders	Common	decreased white blood cell count[#] decreased haemoglobin[#] decreased platelet count[#]
Immune system disorders	Uncommon	Immune reactivation syndrome
Metabolism and nutrition disorders	very common	increased total cholesterol (fasted) [#] increased LCL cholesterol (fasted) [#]
	Common	decreased appetite

		increased triglycerides (fasted) #
Psychiatric disorders	very common	insomnia#
	Common	abnormal dreams depression* sleep disorders depressed mood
Nervous system disorders	very common	headache* dizziness
	Common	somnolence
Gastrointestinal disorders	very common	nausea increased pancreatic amylase#
	Common	abdominal pain* vomiting increased lipase# abdominal discomfort dry mouth
Hepatobiliary disorders	very common	Increased transaminases#
	Common	Increased bilirubin#
Skin and subcutaneous tissue disorders	Common	rash*
General disorders and administration site conditions	Common	fatigue

BR = background regimen
N = number of subjects

* In the week 96 analysis of the Phase III controlled trials ECHO and THRIVE, the most frequently reported adverse drug reactions (ADRs) (≥ 2%) that were at least of moderate intensity were depression (4.1%), headache (3.5%), insomnia (3.5%), rash (2.3%), and abdominal pain (2.0%).

Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, reported in EDURANT-treated patients from the 96 week pooled data from the ECHO and THRIVE trials were increased pancreatic amylase (3.8%), increased AST (2.3%), increased ALT (1.6%), increased LDL cholesterol (fasted, 1.5%), decreased white blood cell count (1.2%), increased lipase (0.9%), increased bilirubin (0.7%), increased triglycerides (fasted, 0.6^), decreased haemoglobin (0.1%), decreased platelet count (0.1%), and increased total cholesterol (fasted, 0.1%).

No new ADR terms were identified in adult patients in the Phase III ECHO and THRIVE trials between 48 weeks and 96 weeks nor in the Phase IIb TMC278-C204 trial through 240 weeks.

Laboratory abnormalities
In the EDURANT arm in the week 96 analysis of the Phase III ECHO and THRIVE trials, mean change from baseline in total cholesterol (fasted) was 5 mg/dl, in HDL cholesterol (fasted) 4 mg/dl, in LDL cholesterol (fasted) 1 mg/dl, and in triglycerides (fasted) -7 mg/dl.

In the pooled Phase III ECHO and THRIVE trials, serum creatinine increased minimally over 96 weeks of treatment with EDURANT. Most of this increase occurred within the first four weeks of treatment, with a mean change of 0.1 mg/dl (range: -0.3 mg/dl to 0.6 mg/dl) observed overall. In subjects who entered the trials with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in subjects with normal renal function. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate and no subjects discontinued treatment due to increases in serum creatinine. Creatinine increases were comparable by background N(t)RTIs.

In the pooled Phase III ECHO and THRIVE trials, at week 96, there was an overall mean change from baseline in basal cortisol of -19.1 (-30.85; -7.37) nmol/l in the EDURANT arm and of -0.6 (-13.29; 12.17) nmol/l in the efavirenz arm. At week 96, the mean change from baseline in ACTH-
stimulated cortisol levels was lower in the EDURANT group (+18.4 ± 8.36 nmol/l) than in the efavirenz group (+54.1 ± 7.24 nmol/l). Mean values for both basal and ACTH-stimulated cortisol values at week 96 were within the normal range. These changes in adrenal safety parameters were not clinically relevant. There were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.

Description of selected adverse reactions
Lipodystrophy
CART has been associated with redistribution of body fat (lipodystrophy) in HIV infected patients, including loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump) (see Special Warnings and Precautions for Use).

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Grave's disease) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment (see Special Warnings and Precautions for Use).

Paediatric population (12 to less than 18 years of age)
The safety assessment is based on the week 48 analysis of the single-arm, open-label, Phase 2 trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1 infected patients 12 to less than18 years of age and weighing at least 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral agents (see section 5.1). The median duration of exposure for patients was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.
Most ADRs were Grade 1 or 2. The most common ADRs (all grades, greater than or equal to 10%) were headache (19.4%), depression (19.4%), somnolence (13.9%), and nausea (11.1%). No grade 3-4 laboratory abnormalities for AST/ALT or grade 3-4 ADRs of transaminase increased were reported.

The safety and efficacy of EDURANT in children aged < 12 years have not yet been established.
No data are available.

Other special populations
Patients co-infected with hepatitis B and/or hepatitis C virus
In patients co-infected with hepatitis B or C virus receiving EDURANT, the incidence of hepatic enzyme elevation was higher than in patients receiving EDURANT who were not co-infected. This observation was the same in the efavirenz arm. The pharmacokinetic exposure of rilpivirine in co-infected patients was comparable to that in patients without co-infection.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Overdose
There is no specific antidote for overdose with EDURANT. Human experience of overdose with EDURANT is limited. Treatment of overdose with EDURANT consists of general supportive measures including monitoring of vital signs and ECG (QT interval) as well as observation of the clinical status of the patient. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since rilpivirine is highly bound to plasma protein, dialysis is unlikely to result in significant removal of the active substance.

PHARMACEUTICAL PARTICULARS
List of Excipients
Tablet core
Lactose monohydrate
Croscarmellose sodium
Povidone K30
Polysorbate 20
Silicified microcrystalline cellulose
Magnesium stearate

Tablet coating
Lactose monohydrate
Hypromellose 2910 6 mPa.s
Titanium dioxide
Polyethylene glycol 3000
Triacetin

Incompatibilities
Not applicable.

Shelf Life
36 months

Special Precautions for Storage
Do not store above 300C.

Store in the original bottle in order to protect from light.

Keep out of reach of children.

Instructions for Use and Handling
No special requirements.

How Supplied
EDURANT™ film-coated tablet 25mg
Box, 1 bottle @ 30 tablet
Reg. No.: DKI1410901017A1

Harus dengan resep dokter

Manufactured by Janssen-Cilag S.p.A., Latina, Italy
Imported and distributed by PT Soho Industri Pharmasi
Jl. Pulogadung No. 6, Kawasan Industri Pulogadung, Jakarta 13920, Indonesia
Phone (021) 460-5550

For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935 3935

Based on SmPC August 2017 + RLCP + Paediatric indication